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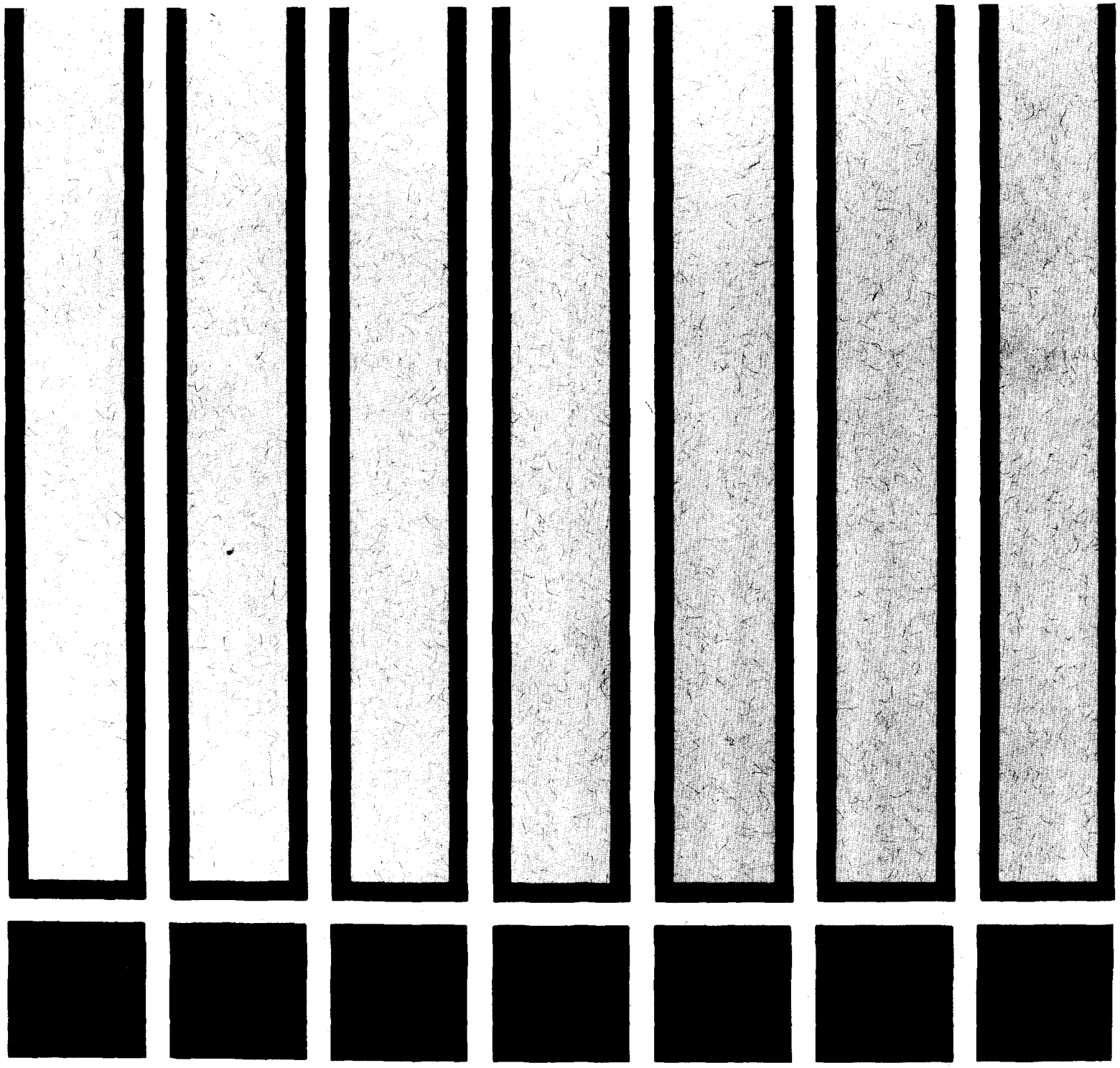

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service / Center for Disease Control
National Institute for Occupational Safety and Health

criteria for a recommended standard....

OCCUPATIONAL EXPOSURE TO

EPICHLOROHYDRIN

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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National Institute for Occupational Safety and Health
SEPTEMBER 1976

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

HEW Publication No. (NIOSH) 76-206

PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. The National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the health effects of exposure. The Secretary of Labor will weigh these recommendations along with other considerations such as feasibility and means of implementation in developing regulatory standards.

It is intended to present successive reports as research and epidemiologic studies are completed and as sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on epichlorohydrin by members of my staff and the valuable constructive comments by the Review Consultants on Epichlorohydrin, by the ad hoc committees of the American Conference of Governmental Industrial Hygienists and the American Occupational Medicine Association, and by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine. The NIOSH

recommendations for standards are not necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on epichlorohydrin. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.

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The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for epichlorohydrin. The Division review staff for this document consisted of J. Henry Wills, Ph.D., Howard Spencer, Ph.D., Seymour Silver, Ph.D., and Frank L. Mitchell, D.O.

Stanford Research Institute (SRI) developed the basic information for consideration by NIOSH staff and consultants under contract No. CDC-99-74-31. Jerry LR Chandler, Ph.D., had NIOSH program responsibility and served as criteria manager.

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CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN OCCUPATIONAL EXPOSURE STANDARD FOR EPICHLOROHYDRIN

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I. RECOMMENDATIONS FOR AN EPICHLOROHYDRIN STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to epichlorohydrin in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and safety of employees for up to a 10-hour workday, 40-hour workweek, over a working lifetime. Compliance with all sections of the standard should prevent adverse effects produced by exposure of employees to epichlorohydrin. Although the workplace environmental limits are considered to be safe levels based on current information, they should be regarded as the upper boundary of exposure, and every effort should be made to maintain exposure as low as is technically feasible. The standard is measurable by techniques that are available and there is sufficient technology to permit compliance with the recommended standard. The standard will be subject to review and revision as necessary.

These criteria and the recommended standard apply to exposure of employees to solid, liquid, or gaseous 3-chloro-1,2-epoxypropane, hereafter referred to as "epichlorohydrin," either alone or in combination with other substances. Synonyms for epichlorohydrin include 1-chloro-2,3-epoxypropane, (chloromethyl)ethylene oxide, chloromethyloxirane, chloropropylene oxide, gamma-chloropropylene oxide, 3-chloro-1,2-propylene oxide, 2-chloromethyl-oxirane, alpha-epichlorohydrin, epichlorhydrin, and epichlorophydrin.

"Occupational exposure to epichlorohydrin" is defined as exposure to airborne epichlorohydrin at concentrations exceeding the action level. The

"action level" is defined as one-half of the recommended time-weighted average (TWA) environmental concentration for epichlorohydrin. Exposure to airborne epichlorohydrin at concentrations equal to or less than one-half of the workplace environmental limit, as determined in accordance with Section 8, will not require adherence to the following sections except for 2, 3, 4(a), 5(a,b,c,d), 6, and 7. If exposure to other chemicals also occurs, provisions of any applicable standard for the other chemicals shall also be followed.

Section 1 - Environmental (Workplace Air)

(a) Concentration

Occupational exposure to epichlorohydrin shall be controlled so that employees are not exposed to epichlorohydrin at concentrations greater than 2 milligrams per cubic meter of air (approximately 0.5 parts per million parts of air by volume) determined as a TWA concentration for up to a 10-hour workday, 40-hour workweek, with a ceiling concentration of 19 milligrams per cubic meter of air (approximately 5 parts per million parts of air by volume) as determined by a sampling time of 15 minutes.

(b) Sampling and Analysis

Procedures for sampling and analysis of environmental samples and calibration of equipment shall be as provided in Appendices I and II, or by any methods shown to be at least equivalent, in accuracy, sensitivity, and precision to the methods specified.

Section 2 - Medical

Medical surveillance shall be made available to all persons subject to occupational exposure to epichlorohydrin as described below:

(a) Preplacement medical examinations shall include:

(1) Comprehensive medical and work histories.

(2) Complete physical examination, giving particular attention to the kidneys, liver, respiratory tract, and hematopoietic system. Additionally, employees shall be evaluated for complaints and evidence of eye, mucous membrane, or skin irritation. Further tests, such as determinations of the concentrations of serum glutamic-pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), and lactic dehydrogenase (LDH), may be considered by the responsible physician.

(3) An evaluation of the ability of the worker to use respirators.

(b) Periodic examinations shall be made available on an annual basis. These examinations shall include, but shall not be limited to:

(1) Interim medical and work histories.

(2) Physical examination as outlined in paragraph (a) (2) of this section. The responsible physician shall consider administering appropriate organ function tests.

(c) Proper medical management shall be provided for employees overexposed to epichlorohydrin. When there is known or suspected overexposure to epichlorohydrin, immediate first-aid measures shall be followed by prompt medical evaluation and followup assistance. First aid shall include removal of the employee from the area of excessive epichlorohydrin exposure, restoration of, or assistance in, breathing by

trained personnel, and treatment of chemical burns.

(d) The responsible physician shall advise the worker that available information indicates that large doses of epichlorohydrin induce antifertility effects on rats; however, no effects on potency have been found. The relevance of this study to male or female workers has not yet been determined. It does, however, indicate that employers and workers should attempt to minimize exposures to epichlorohydrin whenever possible. If the physician becomes aware of any adverse effects on the reproductive systems of workers exposed to epichlorohydrin, the information shall be forwarded to the Director, National Institute for Occupational Safety and Health, as promptly as possible.

(e) Pertinent medical records shall be maintained and made available to the designated medical representatives of the employer, of the employee or former employee, of the Secretary of Labor, and of the Secretary of Health, Education, and Welfare. These records shall be retained for 20 years following the employee's last occupational exposure to epichlorohydrin.

Section 3 - Labeling and Posting

(a) Labeling

Containers of epichlorohydrin shall carry a label stating:

EPICHLOROHYDRIN

POISON! FLAMMABLE!

SKIN CONTACT CAUSES DELAYED BURNS

Avoid contact with eyes, skin, and clothing.
Avoid breathing vapor.
Use only with adequate ventilation.
Keep away from heat and open flame.
Keep container closed.
Do not take internally.

First Aid: In case of skin contact, immediately remove all contaminated clothing, including footwear, wash skin with plenty of water for at least 15 minutes and call a physician. In case of eye contact, flush eyes with water for 15 minutes and call a physician.

(b) Posting

Areas where epichlorohydrin is manufactured, stored, used, or handled shall be posted with a sign reading:

EPICHLOROHYDRIN

POISON! FLAMMABLE!

SKIN CONTACT CAUSES DELAYED BURNS
VAPOR IRRITATING TO EYES
HARMFUL IF INHALED OR SWALLOWED

The sign shall be printed both in English and in the predominant language of non-English-reading workers, if any; the employer shall use these or other equally effective means to ensure that all employees know the hazards associated with epichlorohydrin and the locations of areas in which there is likely to be occupational exposure to epichlorohydrin.

Section 4 - Personal Protective Equipment

(a) Protective Clothing

(1) Chemical safety goggles and face shields shall be

provided by the employer and shall be worn during any operation in which epichlorohydrin may splash into the eyes. Suitable eye protective devices shall conform to 29 CFR 1910.133.

(2) Aprons, suits, boots, or face shields shall be worn when needed to prevent skin contact with liquid epichlorohydrin. The protective clothing for this purpose shall be made of impervious material, such as polyethylene, polypropylene, or polyvinyl chloride (PVC). Use of protective clothing made of neoprene, rubber, or leather is unsuitable.

(b) Respiratory Protection

Engineering controls shall be used to maintain epichlorohydrin concentrations below the recommended environmental limits. Such control equipment shall be sparkproof. Compliance with the permissible exposure limit may not be achieved by the use of respirators except during the time necessary to install or test the required engineering controls, for nonroutine maintenance or repair activities in which brief exposures at concentrations in excess of the recommended limits may occur, and during emergencies when air concentrations of epichlorohydrin may exceed the recommended limits.

When a respirator is permitted by paragraph (b) of this section, it shall be selected and used pursuant to the following requirements:

(1) For the purpose of determining the type of respirator to be used, the employer shall measure, when possible, the concentration of airborne epichlorohydrin in the workplace initially and thereafter whenever process, worksite, or control changes occur which are likely to increase the epichlorohydrin concentrations; this requirement does not apply when only atmosphere-supplying, positive pressure respirators are used. The

employer shall ensure that no worker is exposed to epichlorohydrin in excess of the recommended workplace environmental limits because of improper respirator selection, fit, use, or maintenance.

(2) A respiratory protection program meeting the requirements of 29 CFR 1910.134 shall be established and enforced by the employer.

(3) The employer shall provide respirators in accordance with the provisions of both Table I-1 and 30 CFR 11 and shall ensure that the employee uses the respirator provided.

(4) Respirators specified for use in higher concentrations of epichlorohydrin may be used in atmospheres of lower concentrations.

(5) The employer shall ensure that respirators are adequately cleaned, and that employees are instructed in the use and the testing for leakage of respirators assigned to them.

(6) Where an emergency which could result in employee injury from overexposure to epichlorohydrin may develop, the employer shall provide respiratory protection as listed in Table I-1.

TABLE I-1

RESPIRATOR SELECTION GUIDE

Maximum Use Concentration	Respirator Type
Less than or equal to 25 ppm	(1) Gas mask with chin-style or front- or back-mounted organic vapor canister (2) Type C supplied-air respirator operated in the pressure-demand. (positive pressure) or continuous-flow mode
Less than or equal to 100 ppm	(1) Gas mask (full facepiece) with chin-style or front-mounted organic vapor canister with impervious plastic cover for head and neck (2) Type C supplied-air respirator operated in the pressure-demand (positive pressure) or continuous-flow mode with a full facepiece and impervious plastic cover for head and neck
Less than or equal to 1,000 ppm	Type C supplied-air respirator with hood, helmet, or suit operated in the continuous-flow mode
Greater than 1,000 ppm	(1) Self-contained breathing apparatus with full facepiece operating either in the demand (negative pressure) mode or in the pressure-demand (positive pressure) mode worn under an impervious plastic suit with headpiece (2) Combination Type C supplied-air respirator with full facepiece operated in the pressure-demand (positive pressure) mode and an auxiliary self-contained air supply worn under an impervious plastic suit with headpiece

TABLE I-1 (CONTINUED)

RESPIRATOR SELECTION GUIDE

Maximum Use Concentration	Respirator Type
Emergency (no concentration limit)	(1) Self-contained breathing apparatus in the pressure-demand (positive pressure) mode with full facepiece (2) Combination supplied-air respirator with an auxiliary self-contained air supply and full facepiece operated in the pressure-demand (positive pressure) mode
Escape (no concentration limit)	(1) Gas mask (full facepiece) with chin- or front-mounted organic vapor canister (2) Self-contained breathing apparatus with full facepiece operated either in the demand (negative pressure) mode or in the pressure-demand (positive pressure) mode

Section 5 - Informing Employees of Hazards from Epichlorohydrin

(a) Each employee working in an area where exposure to epichlorohydrin is likely, shall be informed of the signs and symptoms of overexposure, emergency and first-aid procedures, the hazards of chronic exposure, and precautions to ensure safe use of epichlorohydrin and to minimize exposure. All information shall be posted in the workplace and shall be readily accessible to the employee.

(b) Employers shall ensure that all such employees have current knowledge of job hazards, maintenance procedures, and cleanup methods, and

that they know how to use respiratory protective equipment and protective clothing.

(c) Employees and members of emergency teams who work near epichlorohydrin systems or containers where a potential for emergencies exists shall participate in periodic drills simulating emergencies appropriate to the work situation. Drills shall be held at intervals not greater than 6 months. Drills should include, but should not be limited to:

Evacuation procedures.
Handling of spills and leaks, including decontamination.
Location and use of emergency firefighting equipment, and handling of epichlorohydrin systems or containers in case of fire.
First-aid and rescue procedures, including prearranged procedures for obtaining emergency medical care.
Location, use, and care of protective clothing and respiratory protective equipment.
Location of shut-off valves or switches.
Location, purpose, and use of safety showers and eye-wash fountains.
Operating procedures including communication procedures.
Entry procedures into confined spaces.

Deficiencies noted during drills shall be included in the continuing educational program together with the required remedial actions. Records of drills and training sessions shall be kept and made available for inspection by authorized personnel upon request.

(d) Information as required shall be recorded on the "Material Safety Data Sheet" shown in Appendix III, or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Engineering controls, such as process enclosure or local

exhaust ventilation, shall be used to maintain epichlorohydrin concentrations at or within the recommended workplace environmental limits. Ventilation systems shall be designed to prevent the accumulation or recirculation of epichlorohydrin in the workplace and to remove epichlorohydrin from the breathing zones of exposed workers. When used, exhaust ventilation systems discharging to outside air must conform with applicable local, state, and federal air pollution regulations. Ventilation systems shall undergo regular preventive maintenance and cleaning to ensure maximum effectiveness, which shall be verified by periodic airflow measurements. Records of these measurements shall be maintained for at least 1 year.

(b) When an operation involves the use of epichlorohydrin in an open vessel, which is not part of an isolated system, continuous local exhaust ventilation shall be provided so that air movement is always from the work areas to the operation. Exhaust air shall not be discharged in the work areas and clean makeup air shall be introduced in sufficient volume to maintain the correct operation of the local exhaust system. Containers of epichlorohydrin shall be labeled in accordance with Section 3 and shall be kept tightly closed at all times when not in use. Storage provisions are listed in 29 CFR 1910.106(a)19(iii). Containers shall be protected from heat, corrosion, mechanical damage, and sources of ignition.

(c) Any spilled epichlorohydrin shall be promptly cleaned up. During cleanup operations, complete skin and respiratory protective equipment shall be used. After a cleanup operation, the employee shall be required to shower upon removing the protective equipment. If epichlorohydrin is spilled on shoes made of leather, canvas, rubber, or of

any other permeable material, the shoes shall be rendered unusable and discarded. If clothing is contaminated with epichlorohydrin, it shall be removed promptly and laundered thoroughly before reuse.

(d) Appropriate regulations for Class IC flammable liquids are provided in 29 CFR 1910.106.

(e) Prior to maintenance work, sources of epichlorohydrin vapor shall be eliminated to the extent feasible. The employees shall be provided with appropriate skin and respiratory protective equipment.

(f) Confined Spaces

(1) Entry into confined spaces, such as tanks, pits, tank cars, barges, process vessels, and tunnels, shall be controlled by a permit system. Permits shall be signed by an authorized employer representative certifying that preparation of the confined space, precautionary measures, and personal protective equipment are adequate, and that precautions have been taken to ensure that the prescribed procedures will be followed.

(2) Confined spaces which have contained epichlorohydrin shall be inspected and tested for oxygen deficiency, epichlorohydrin, and other contaminants, and, prior to entry by the employee, they shall be thoroughly ventilated, cleaned, and washed.

(3) Inadvertent entry of epichlorohydrin into the confined space while work is in progress shall be prevented by disconnecting and blocking of epichlorohydrin supply lines or by other appropriate means.

(4) Confined spaces shall be ventilated appropriately while work is in progress to keep the concentration of epichlorohydrin at or below the recommended environmental limits and to ensure an adequate supply of oxygen.

(5) Individuals entering confined spaces where they may be exposed to epichlorohydrin shall wear either a combination Type C supplied-air respirator operated in the continuous-flow (positive pressure) mode or an auxiliary breathing air supply operated in the pressure-demand (positive pressure) mode equipped with a full facepiece, or a self-contained breathing apparatus operated in the pressure-demand (positive pressure) mode. Each individual shall also wear a suitable harness with lifelines tended by another employee outside the space who shall also be equipped with the necessary protective equipment, including a self-contained breathing apparatus which operates in the pressure-demand (positive pressure) mode and has a full facepiece. Communication (visual, voice, signal line, telephone, radio, or other suitable means) shall be maintained by the standby person with the employees inside the enclosed spaces.

(g) For all work areas where epichlorohydrin is used, procedures as specified in this section, as well as any other procedures appropriate for a specific operation or process, shall be formulated in advance. Employees shall be comprehensively instructed in the implementation of emergency procedures.

(1) Procedures shall include prearranged plans for obtaining emergency medical care and for transportation of injured workers to medical facilities.

(2) Firefighting procedures shall be established and drills conducted. These shall include procedures for emergencies involving fire and release of epichlorohydrin vapor. In case of fire, epichlorohydrin sources shall be shut off or removed as soon as feasible. Containers of epichlorohydrin shall be removed or cooled with water spray as soon as

feasible. Chemical foam, carbon dioxide, or dry chemicals shall be used for extinguishing epichlorohydrin fires. Proper respiratory protective devices and protective clothing shall be worn to protect against epichlorohydrin, acid gases, and other combustion products of epichlorohydrin.

(3) Approved eye, skin, and respiratory protective devices as specified in Section 4 shall be used by all personnel who are essential to emergency operations.

(4) During emergencies, employees not essential to the emergency operations shall be evacuated. A warning system informing the employees of the evacuation shall be established. Boundaries of areas where the emergency occurred shall be delineated, posted, and secured as soon as feasible. Entry into hazardous areas shall be prohibited to employees not essential to the emergency operations.

(5) Personnel trained and knowledgeable in the safety procedures and adequately protected against the attendant hazards shall shut off sources of epichlorohydrin, clean up spills, and immediately repair leaks.

Section 7 - Sanitation

(a) Food preparation, storage, dispensing, and eating shall be prohibited in posted work areas.

(b) Smoking shall be prohibited in posted work areas.

(c) Safety showers and eyewash fountains shall be installed in and adjacent to posted work areas.

(d) Shower facilities shall be made available to employees who may have occupational exposure to epichlorohydrin.

Section 8 - Monitoring and Recordkeeping Requirements

Workers will not be considered to have occupational exposure to epichlorohydrin if the environmental concentrations, as determined by an industrial hygiene survey conducted within 6 months of the promulgation of a standard, do not exceed one-half the recommended TWA environmental limit, ie, the action level. Surveys shall be repeated at least once every 3 months and within 30 days after any process change likely to result in increases of airborne concentrations of epichlorohydrin. Records of these surveys, including the basis for concluding that airborne concentrations of epichlorohydrin are at or below the action level, shall be maintained. If the survey indicates that airborne concentrations of epichlorohydrin exceed the action level, then the following requirements apply:

(a) Personal Monitoring

(1) A program of personal monitoring shall be instituted to identify and measure, or permit calculation of, the exposure of all employees who are occupationally exposed to epichlorohydrin. Interim monitoring of employee exposure to airborne concentrations of epichlorohydrin shall be conducted at least every 3 months. If monitoring of an employee's exposure to epichlorohydrin reveals that the employee is exposed at concentrations in excess of the recommended TWA environmental limit, the exposure of that employee shall be measured at least once every 30 days, control measures shall be initiated, and the employee shall be notified of the exposure and of the control measures being implemented to

correct the situation. Such monitoring shall continue until two consecutive samplings, at least 1 week apart, indicate that the employee's exposure no longer exceeds the TWA environmental limit recommended in Section 1(a). Quarterly monitoring may then be resumed.

(2) In all personal monitoring, samples of airborne epichlorohydrin that will provide upon analysis an accurate representation of the concentration of epichlorohydrin in the air the worker breathes shall be collected. Procedures for sampling, calibration of equipment, and analysis of epichlorohydrin in samples shall be as provided in Section 1(b).

(3) For each TWA determination, a sufficiently large number of samples shall be taken to characterize each employee's exposure during each workday. Variations in work and production schedules shall be considered in deciding when samples are to be collected. The number of representative TWA determinations for an operation or process shall be based on the variations in location and job functions of employees in relation to that operation or process.

(b) Recordkeeping Procedures

Records shall be maintained and shall include sampling and analytical methods, type of respiratory protective device used, and TWA and ceiling concentrations found. Each employee shall have access to data on personal environmental exposures and records of such data shall be included in his medical records. Pertinent records of required medical examinations, including records of occupational accidents, and environmental exposures within the workplace shall be maintained for 20 years after the worker's last occupational exposure to epichlorohydrin and shall be available to the

designated medical representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational diseases arising from exposure to epichlorohydrin. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health of workers from exposure to hazardous chemical and physical agents. These criteria for a standard for epichlorohydrin are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to the processing, manufacture, and use of, or other occupational exposure to, epichlorohydrin as applicable under the Occupational Safety and Health Act of 1970. The standard was not designed for the population-at-large, and any extrapolation beyond occupational exposures is not warranted. It is intended to (1) protect against the development of acute and chronic effects of epichlorohydrin exposure, (2) protect against local effects on the skin, (3) be measurable by techniques that are available to industry and government agencies, and (4) be

attainable with existing technology.

The development of the criteria for the recommended standard for occupational exposure to epichlorohydrin has elucidated the need for further research in the following areas: (1) further epidemiologic studies of employees exposed to epichlorohydrin, (2) animal studies designed to determine the cumulative effects from inhalation of airborne epichlorohydrin at concentrations below 5 ppm, (3) studies on the mutagenic effects of epichlorohydrin in mammals, and (4) animal studies to investigate the carcinogenic effects from epichlorohydrin inhalation. To fill these information gaps, a concerted effort is required by those people who are involved with the health and safety of employees exposed to epichlorohydrin.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Epichlorohydrin (formula weight 92.53) is a colorless liquid at room temperature with a distinctive odor described as "ethereal," "chloroform-like," and "garlic-like." [1] Its boiling point is 116.4 C and the vapor pressure at 29 C is 20 mmHg. [2] The low latent heat of vaporization of epichlorohydrin (9,060 cal/mole) [3] contributes to the rapid evaporation of spills. Other physical properties are given in Table XIII-1. [2,4,5]

Epichlorohydrin is a reactive molecule which may form covalent bonds under biologic conditions. [6,7] In reactions with alcohols, amines, thiols, and other nucleophilic biochemical constituents of the cell, the epoxide ring opens and forms a new, stable, covalent carbon-hetero atom bond as shown in the reaction in Figure XIII-1. The initial reaction product may undergo a second nucleophilic reaction to form stable, covalent cross-linking bonds between two molecules either by direct displacement of the chlorine atom or through the formation of an unstable, short-lived cyclic intermediate. [8] These cross-linking bonds may have a high degree of chemical stability, such as is typically found in epoxy resins. [4] The chemical characteristic of epichlorohydrin to react as a bifunctional alkylating agent is an intrinsic property of its molecular structure.

Biologic organisms contain many different chemical nucleophiles, such as alcohols, acids, amines, sulfhydryls, carbohydrates, lipids, proteins, ribonucleic acids, and deoxyribonucleic acids. [9] Epichlorohydrin has a greater tendency to react with more readily polarized groups, such as sulfhydryl groups, than with less readily polarized groups, such as

hydroxyls. The half-life of epichlorohydrin in water at a pH of 7 is 36.3 hours. [6] Although the half-life of epichlorohydrin in biologic tissues is not known, the known presence of large numbers of nucleophiles in tissue suggests that it is shorter than the half-life in water. Mammalian enzymes which catalyze the hydrolysis of epichlorohydrin, or otherwise degrade it, would further decrease the biologic half-life. Under hypothetical, constant, nonlethal exposure conditions, a steady-state concentration of epichlorohydrin would eventually be achieved in all tissues, resulting in a steady-state rate of alkylation of tissue constituents. For reviews of the pertinent literature, the reader is referred to Ross [6] and Loveless. [7]

Extent of Exposure

Epichlorohydrin is commercially synthesized from allyl chloride, [12] allyl alcohol, [12] dichlorhydrin-glycerine, [11,12] or propylene. [13] The total US production of epichlorohydrin was about 550 million pounds in 1975. [14] Projected expansion plans, if accomplished, would increase total production to 715 million pounds by 1978. [14]

In 1969, the total US production of crude epichlorohydrin was about 322 million pounds. [12] An estimated 58% of this was used in the manufacture of synthetic glycerine and 42% was processed to refined epichlorohydrin. [12] Refined epichlorohydrin is used in the manufacture of epoxy resins, surface active agents, pharmaceuticals, insecticides, agricultural chemicals, textile chemicals, coatings, adhesives, ion-exchange resins, solvents, plasticizers, [15] glycidyl esters, [16] ethynyl-ethylenic alcohol, [17] and fatty acid derivatives. [16] Most

epoxy resin is synthesized by alkylating bisphenol A with epichlorohydrin. [4]

A number of cases of dermal sensitization have been reported in workers in the epoxy resin-producing and resin-using industries. [18-20] Attempts to identify the causative agents have been only partially successful. [18-20] Traces of free epichlorohydrin have been found in the resin in the USSR [21] and Sweden (S Fregert, written communication, September 1975); however, a few case reports have indicated that epichlorohydrin itself is probably not the responsible chemical. [19,22]

In the United States, a hazard survey was conducted by NIOSH around electronic component-molding operations where several different epoxy resins were used. [23] Most of these resins were made from bisphenol A and epichlorohydrin and had to be heated prior to use. Environmental monitoring using charcoal-tube and gas chromatography indicated that epichlorohydrin was not present in the air in any detectable quantity. The lowest limit of detection was 0.008 mg or approximately 0.02 mg/cu m (0.005 ppm).

NIOSH estimates that 50,000 employees may be exposed to epichlorohydrin in the United States.

Historical Reports

The first report on epichlorohydrin toxicity was made by Von Kossa [24] in 1898. He found that, following dermal contact, epichlorohydrin induced transitory burning and slight irritation in human subjects. One person with sensitive skin developed an eczema lasting 3 weeks following a 1-hour application of 0.5 g of epichlorohydrin. Von Kossa [24] also

investigated the effects of epichlorohydrin on a dog, rabbits, pigeons, and frogs to evaluate its usefulness as an anesthetic agent. A dog was reported to have received a total of 381 g of epichlorohydrin within 7 days by an unspecified route and to have died on the eighth day. A swollen liver and edema of the superficial abdominal tissues were observed. Subcutaneous injection of 1.16 g of epichlorohydrin into a rabbit produced labored breathing, cyanosis, narcosis, and death in about an hour. At autopsy, emphysematous and hyperemic lungs were evident. Daily subcutaneous injections of 0.15 g of epichlorohydrin were administered to another rabbit for 7 days, and the animal died on the eighth day. Hemorrhages in the stomach, especially in the fundus, along with a seared appearance of the adjacent mucous membrane in the stomach were observed at autopsy. An unspecified amount of albumin was detected in the urine. When a cloth soaked in 5 cc of epichlorohydrin was placed next to a pigeon in a jar, sneezing, labored breathing, body trembling, narcosis, and death resulted within an hour. Another pigeon injected intramuscularly with 0.07 g of epichlorohydrin on 2 consecutive days died on the second day. Autopsy revealed edema at the injection site, plethoric meningeal blood vessels, intestinal inflammation, and hemorrhage. The dorsal lymph sacs of two frogs were each injected with 0.15 g of epichlorohydrin. Exophthalmos and irregular respiration were observed. Although apparent recovery occurred within an hour after injection, both frogs died about 5 hours later. A third frog, whose heart had been exposed, was injected similarly with 0.15 g of epichlorohydrin. The cardiac rate decreased from 40 to 34 beats/minute within 20 minutes, and the animal died within 6 hours of epichlorohydrin administration. Von Kossa [24] believed that the severe

irritating action of epichlorohydrin on the gastrointestinal tract would make it unsuitable as an anesthetic. He also indicated that its strong depressant effects on the heart and respiration would make it unsatisfactory for any use in medicine. The narcotic and the persisting dermal effects of epichlorohydrin, as well as the effects on respiration, liver, and gastrointestinal tract reported by Von Kossa [24] in 1898, have been confirmed repeatedly by other investigators. [25-32] These effects are further discussed in Animal Toxicity.

Effects on Humans

In 1964, Schultz [33] reported the case of a 39-year-old temporary worker exposed to a gust of epichlorohydrin from a presumably empty tank. He immediately experienced irritation of the eyes and throat, followed by facial swelling, nausea, vomiting, headache, and dyspnea. The following day, he went to the clinic where his liver was found to be enlarged. Two days after the exposure, a slight jaundice associated with a serum bilirubin of 3.44 mg% was observed. The accepted range of normal values for the concentration of bilirubin in serum is 0.1-1.2 mg%. [34] After 18 days, his jaundice had subsided, but his liver was still slightly enlarged. Five months later, the same hospital conducted a medical evaluation of the man; the major findings were bronchitic alterations in the right lung, elevated blood pressure, and liver damage. Liver function was still abnormal, as indicated by elevated amounts of urobilin and urobilinogen in the urine. Eight months later, the man still had a serum bilirubin of 2.6 mg% and abnormal amounts of urobilin and urobilinogen in the urine. Nearly 2 years after the accident, the author [33] examined this worker. A liver

biopsy indicated fatty changes, while delayed sulfobromophthalein (BSP) elimination, increased galactose excretion, and increased concentrations of urinary bile pigments indicated altered liver function. Hypertension (degree not reported) and chronic asthma-like bronchitis also were present. The author reported that other possible causes of liver damage, such as nutritional defects, alcoholism, diabetes, tuberculosis, and prior liver disease, were explored and ruled out. Although the author concluded that the liver damage and the asthma-like bronchitis were induced by epichlorohydrin poisoning, a possibility remains that the liver damage had some other cause. Hypertension was judged to be independent of the epichlorohydrin exposure. No renal damage was found. It is evident from this report [33] that irritation of eyes and throat, facial swelling, nausea, vomiting, headache, and dyspnea are the immediate effects of acute overexposure to epichlorohydrin on humans. However, it is not possible to draw any general conclusions on chronic effects resulting from an acute epichlorohydrin inhalation from this report on a single subject.

A case of a 53-year-old worker who was exposed for about 30 minutes to fumes of epichlorohydrin from a leaking condensor was briefly reported by Thoburn (written communication, May 1976). Several hours after the exposure, the worker complained of burning of his nose and throat, cough, and chest congestion. Other symptoms included running nose, eye tenderness, and headache followed by nausea. The man was hospitalized briefly. The symptoms faded within 3 to 4 days, without definite sequelae except that the man reported that he had more frequent infections of the upper respiratory tract than he had experienced previously. He also complained that these infections were often followed by productive

after the exposure, measurements indicative of air trapping in the lungs (increase of residual volume by 40% and arterial pO2 of 77 mm of Hg, instead of the normal 95 mm) were made. While the report is indicative of the hazards associated with acute exposures to high but unknown concentrations of epichlorohydrin, quantitative conclusions cannot be drawn from the available information.

In 1970, Ippen and Mathies [35] reported burns resulting from dermal contact with epichlorohydrin in five male workers, aged 19-32 years. On separate occasions, two workers came into contact with mixtures of epichlorohydrin and methanol. Two days after exposure, one worker noticed redness of the hands. By the 3rd day, the symptoms had intensified so that he went to the clinic. He had severe redness, swelling, and red papules on both hands. Under treatment with corticoid ointments and tablets of 3-pyridine methanol, a vasodilator drug, the redness and swelling subsided so gradually that he did not return to work until 22 days after the accident. More than 2 months (73 days) after the accident, he still had a red discoloration of the hands and erythema at the sites of the papules. The second worker wiped up about 1.5 liters of an epichlorohydrin-methanol mixture (2:3) from the floor. Even though he washed his hands with soap and water, he experienced redness and itching of the palms severe enough to require the application of corticoid ointment on the 4th day. He was admitted to the hospital 2 days later because of intensified itching of the palms and edema of the palms, fingers, and backs of his hands. During his 11-day hospital stay, he was treated with iv injections of Reparil (a saponin) and with heparinoid ointment bandages. The redness and swelling gradually diminished, but the skin of his hands

remained rough. The patient did not return for followup examination after leaving the hospital.

A third worker [35] splashed a small amount of epichlorohydrin on his right trouser leg. [32] He experienced a burning sensation on the thigh and observed a slight redness after 10 minutes. He applied a local anesthetic cream. Two days later, because of increased redness and burning, he visited an outpatient clinic. On the anterior side of the thigh, two palm-sized and several small dark-red and extremely dry areas, as though tanned, were observed. The patient was treated with antibacterial ointments as an outpatient. The redness and burning subsided with only moderate residual erythema, so that he was able to return to work after 9 days' absence.

The two remaining incidents involved recurring exposures to epichlorohydrin. [35] A 19-year-old apprentice spilled epichlorohydrin on his shoe and stocking which he removed 6 hours later. Burning, itching, blisters, and skin erosion developed and intensified within the next 2 days. Severe skin erosion (5 cm in diameter) on the dorsum of the foot and painful, enlarged lymph nodes in the groin were evident when he was admitted to a hospital 10 days after the accident. He was effectively treated with penicillin injections, moist bandages, and corticoid ointments and was able to return to work on the 34th day after the accident. Almost 2 years later, he resumed work with epichlorohydrin for 3 days, during which he spilled the liquid on his protective rubber gloves. During the night of the 3rd day after resuming work with epichlorohydrin, he noticed burning, swelling, reddening, and vesiculation on several fingers of both hands. He went to a clinic on the 4th day, was hospitalized for 10 days,

and was treated with metal foil bandages and bland ointments. He returned to work on the 20th day following the reexposure to epichlorohydrin. In a followup examination 8 days later, persistent redness of the affected fingers was evident.

The last of the five case studies dealt with a 32-year-old worker who spilled epichlorohydrin in his right safety shoe. [35] Although he removed the shoe immediately and rinsed his foot with lukewarm water, a spotty redness developed within 2 hours over the ball and the base joint of the large toe. Physiologic saline compresses were applied for 5 days. He returned to work on the 6th day. Eight days later, he again spilled epichlorohydrin into his right shoe. Despite being aware of a slight burning sensation during that afternoon, he returned to work on the following day. On the 3d day after the accident a blister developed, and he went back to the hospital. After treatment with physiologic saline, and later with a salve of unspecified nature for 14 days, he was able to leave the hospital. During his hospital stay, peripheral arteriosclerosis with hyperlipidemia, as evidenced by 1,117 total lipids, 268 total cholesterol, 620 mg% esterified fatty acids, and 368 mg% triglycerides, was diagnosed. Normal values stated in Todd-Sanford Clinical Diagnosis by Laboratory Methods [34] for total lipids, total cholesterol, esterified fatty acids, and triglycerides are 600, 250, 200, and 100 mg%, respectively. The authors concluded that no causative relation between epichlorohydrin exposure and the arteriosclerosis with hyperlipidemia existed, but that the exposures may have had an undesirable effect on the worker's health.

Ippen and Mathies [35] referred to the skin effects from epichlorohydrin as protracted chemical burns and suggested several work

practices to prevent their occurrence. They felt that specific work practices were necessary since epichlorohydrin penetrates rubber and leather. They noted that there was a latent period of several minutes to several hours between contact with epichlorohydrin and its manifestations. The authors drew attention to similar latent periods for burns caused by X-rays or by such alkylating agents as ethylene oxide. The authors [35] recommended that studies of the peripheral vasculature be done as soon as possible after dermal contact with epichlorohydrin to distinguish between sequelae and preexisting vascular alterations. This recommendation was made because of the persistent erythema observed after every accident and the pronounced peripheral arteriosclerosis diagnosed in one patient. No indication of sensitization was reported in the two workers whose contact with epichlorohydrin was repeated. These cases demonstrated that skin exposure to liquid epichlorohydrin can cause severe chemical burns. When skin contact with epichlorohydrin was short, the severity of the burns was much less than when skin contact was prolonged. Therefore, it can be concluded that the intensity of the burns is dependent on the duration and extent of exposure, which control the extent of reaction with cellular constituents.

In 1966, Pet'ko et al [11] investigated the health of workers engaged in the production of epichlorohydrin from dichlorhydrin glycerine (DCG) in Russia. Environmental monitoring for both epichlorohydrin and DCG was done by an unspecified sampling method. In some instances, the epichlorohydrin concentration in air was reported to be 2-14 times greater than its maximum permissible concentration. Neither the measured nor the permissible concentration of epichlorohydrin was reported. In the working zone of the

workers who withdrew samples for analysis from the epichlorohydrin production process, the concentration range in the ambient air was 19-21 mg/cu m or approximately 4.9-5.5 ppm. When workers poured epichlorohydrin into the filling tanks, the concentrations in air reached 12-15 mg/cu m (approximately 3.1-3.9 ppm). During an emergency due to mechanical difficulties, airborne epichlorohydrin concentrations of 210-211 mg/cu m (approximately 54.6-54.9 ppm) occurred. Forty-nine men and 33 women, predominately in the 20-35 age range, who worked in the epichlorohydrin production areas were examined. Medical examinations were directed to assessing the symptoms of the effects on ocular mucous membranes, the skin, and the respiratory, cardiovascular, and nervous systems. Morphologic examinations of peripheral blood, reticulocyte counts, and urinalyses were done. The bilirubin, cholesterol, and protein concentrations in the blood were also determined. Allergic manifestations of unspecified nature were mentioned as being present in some workers with only 2.5-3 years of service in the plant manufacturing epichlorohydrin. Although the authors considered the individual worker's length of service to be unrelated to the nature and frequency of the complaints, they did not report the nature of the complaints. They concluded that no deviations from the normal which could be interpreted in terms of occupational factors, other than two cases of occupational dermatitis, were identifiable. The dermatitis cases were not discussed. Pet'ko et al [11] recommended that further studies be done, and that annual medical examinations by an internist, a dermatologist, and a neuropathologist be given. The authors gave no explanation for including a neuropathologist, nor did they specify the clinical basis for recommending blood and urine examinations.

In 1966, Fomin [28] determined the human olfactory threshold and subthreshold of epichlorohydrin to be 0.3 mg/cu m (approximately 0.08 ppm) and 0.2 mg/cu m (approximately 0.05 ppm), respectively, using an unspecified test method. The effects of epichlorohydrin on the light sensitivity of the eyes were investigated in four volunteer subjects. No significant ocular changes occurred with exposure to epichlorohydrin at a concentration range of 0.2-0.75 mg/cu m (approximately 0.05-0.19 ppm). The concentration of epichlorohydrin in air was determined by using an iodometric method based on oxidation of epichlorohydrin to formaldehyde and further reaction with chromotropic acid. A total of 67 electroencephalographic (EEG) recordings were done in 5 subjects, and the voltage of the spikes of the alpha rhythm was analyzed quantitatively. An epichlorohydrin concentration of 0.3 mg/cu m (approximately 0.08 ppm), the olfactory threshold, caused significant (P value not given) changes in all five subjects. These changes included increased voltage of the spikes of the alpha rhythm in the EEG's of four subjects and decreased voltage in that of the fifth, the latter within 10 minutes after exposure. Epichlorohydrin at a concentration of 0.2 mg/cu m (approximately 0.05 ppm) caused no changes. Unspecified conditioned reflexes were also analyzed but the results were not reported. Although the psychologic and physiologic significances of such changes in the EEG recordings are not clearly defined, the results do indicate that epichlorohydrin is capable of causing changes in the alpha rhythms of the EEG. No other reports of similar findings have been found in the literature.

In 1970, Fregert and Gruvberger [36] studied sensitization and cross-sensitization of epichlorohydrin with propene oxide (propylene oxide) on

skin. With Fregert as the subject, the authors found that, following application for 2 days of patches containing epichlorohydrin diluted to 0.1, 0.5, and 1.0% with ethanol, no immediate effects on the skin were visible, but reactions developed after 8-11 days at all test sites. Retesting with 0.1 and 0.01% epichlorohydrin induced a positive reaction after 2 days to 0.1% epichlorohydrin and resulted in erythema with 0.01% epichlorohydrin. Propene oxide, 0.2% in ethanol, gave a positive reaction when it was applied to skin previously exposed to epichlorohydrin. Negative reactions were obtained with 1-chloropropane (1%), 1-chloro-2-propanol (1%), and ethylene oxide (1%) after application of these compounds to areas where epichlorohydrin had been applied. They concluded that the epoxy group and the three carbon atoms in the chain, but not the chlorine, were necessary for the cross-sensitization capacity. This report lacks experimental details and involved only one subject and, thus, is not a sufficient basis for a general conclusion about sensitization to epichlorohydrin or cross-sensitization to propene oxide.

Jirasek and Kalensky [19] examined 17 workers who developed eczema while working with epoxy resin. To identify the causative agent, they conducted dermal tests using several chemicals including epichlorohydrin. A 1% epichlorohydrin solution in ethanol produced positive reactions in three of the subjects. Experimental details were not reported.

In 1971, a summary sheet drawn by industry [37] stated that 1-hour exposures to epichlorohydrin at a concentration of 20 ppm induced transient burning of the eyes and nasal passages in manufacturing-plant workers, and that a similar exposure at a concentration of 40 ppm caused eye and throat irritation lasting 48 hours. It was further suggested that a concentration

of 100 ppm would be intolerable for even a short period. No details of these exposures were given. In addition, the method by which the epichlorohydrin concentrations were measured or verified was not reported. In the absence of such information, it is reasonable to assume that these observations are derived from accidental occupational exposures to epichlorohydrin.

In 1971, Wexler [38] reported similar information. At a concentration of 20 ppm, exposure to epichlorohydrin resulted in burning of the eyes and nasal mucosa within 1 hour. At a concentration of 40 ppm, the epichlorohydrin-induced throat irritation lasted 48 hours despite immediate medical treatment. Wexler [38] further stated that exposure to epichlorohydrin at concentrations greater than 100 ppm could not be tolerated by humans because of the occurrence of lung edema and kidney lesions. Not enough detail was given to permit adequate evaluation of this paper. The occurrence of severe effects at 100 ppm is supported, however, by the previous report [37] in which it was postulated that exposure at 100 ppm would be intolerable.

A study of 48 employees who had been exposed at least once to epichlorohydrin was reported by Kilian (written communication, June 1976). These people were studied for periods of from 7 days to 13 years after exposure; the mean length of followup was 6.3 years. Blood samples were analyzed for hemoglobin, albumin, globulin, cholesterol, BUN, uric acid, bilirubin and glucose concentrations, and alkaline phosphatase, lactic dehydrogenase, SGOT, and SGPT activities. Hematocrit index and total and differential leukocyte counts were determined also. The various values obtained were compared with those used by the company as normals.

The blood chemistries of two of the employees were all within the normal range. Overall, the most frequently observed changes involved differential leukocyte values. The majority of the percentage of polymorphonuclear leukocytes determinations were below normal for 39 employees and above normal for 4 employees. The majority of the percentage of monocytes determinations were elevated for 35 employees; none had the greater number of the determinations below normal. Because the leukocytic and the monocytic changes were common to 32 of the 48 employees, it is reasonable to assume they are related. However, there is no proof that either was the result of exposure to epichlorohydrin.

A total of 16 employees had the greater number of determinations of percentage of eosinophilic leukocytes that were higher than normal. Total leukocyte counts and hemoglobin concentrations were increased in 15 employees, while fewer total leukocytes and lower hemoglobin concentrations, respectively, were reported for 5 and 8 employees. With respect to enzyme determinations, SGOT activities were decreased in a total of 13 employees and increased in only 1. The other determinations rarely deviated from their respective normal ranges.

In the absence of further details on the extent of epichlorohydrin exposure and individual histories, no general conclusions can be drawn from these data. In the majority of the 48 cases, the deviations from normal ranges were no longer detectable after a few months. In five of the reported cases, however, one or more of the measured values remained outside the normal range from 7 to 13 years after exposure. Reexamination of one of these men about 4.5 months later gave values for the various measurements that were within the normal ranges.

From the available data, it is not possible to attribute these persistent changes solely to epichlorohydrin exposure. The most frequently observed deviations from the normal ranges were a decrease in the percentage of polymorphonuclear leukocytes and an increase in the percentage of monocytes in the total leukocytes count of the blood; even these changes were not consistent in any employee. The data suggest that a detailed study of the medical histories of these individuals and their possible exposure to other chemicals is necessary before the hazards of permanent injury from epichlorohydrin exposure can be evaluated. These results indicate that, despite the finding of mutagenic activity for microorganisms in the urine of people who had been exposed to epichlorohydrin, there is no firm evidence that nonincapacitating exposures to this chemical produce persistant effects on metabolic and homeostatic mechanisms of the human body.

Epidemiologic Study

No published epidemiologic studies on workers exposed to epichlorohydrin were found. Kilian (written communication, April 1976) reported a retrospective morbidity study conducted on 680 DOW Chemical Company employees, the results of which were analyzed by an outside consulting firm. The medical examination data on 507 employees who had been exposed to epichlorohydrin for at least 6 months were presented. The longest term of employment was 16 years, but the majority of the people (exact number not given) were exposed to epichlorohydrin for periods of 5 years or less. Environmental monitoring data were not available, but each employee was classified on the basis of work history and job titles as

having either minimal or moderate exposure. A total of 110 employees were assigned to the moderate-exposure group and 397 to the minimal-exposure group. The measurements of toxic effects were: illness episodes, electrocardiogram (ECG), X-ray examination of the chest, pulmonary function tests, and laboratory measurements such as urinalysis, hemograms, and blood chemistries. Illness, defined as absence of an employee from work for 7 or more days, was classified as either respiratory or nonrespiratory in nature. Urinalysis data included measurements of the presence of protein and erythrocytes in the urine. Hemograms included hematocrit index, white blood cell count, lymphocyte cell count, and eosinophil cell count. Blood chemistry included concentrations of creatinine and BUN, albumin-to-globulin ratio, and lactate dehydrogenase, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT) activities. An attempt was made to correlate any medical abnormalities with the degree of exposure.

In the minimal-exposure group, 213 employees had 1,343 episodes of illness (6.3 illnesses/employee), while in the moderate group 193 illness episodes occurred in 49 employees (4.0 illnesses/employee). Employees in the minimal-exposure group had 254 (39%) respiratory illnesses while employed in the epichlorohydrin-exposure area and 231 (33%) such episodes while employed in other areas. In the moderate-exposure group, 57 (55%) of all illnesses during epichlorohydrin exposure were respiratory and only 24 (27%) were respiratory during nonexposure to epichlorohydrin. The consultants concluded that illness during employment in an epichlorohydrin-exposure area is more likely to be respiratory than one during employment elsewhere.

Examination of the ECG revealed that 5.0% of the employees in the minimal-exposure group and 2.7% in the moderate-exposure group had abnormal records. The consultants concluded that epichlorohydrin exposure had not influenced the ECG records.

Study of pulmonary roentgenograms indicated that, in both the moderate- and minimal-exposure groups, 1.8% contained abnormal findings, such as emphysematous blebs, mild pneumonic infiltration, pneumonia, mild chronic pulmonary fibrosis, minor emphysema, and infiltrative lesions. The consultants noted that, in addition to the same frequency of abnormal X-radiographs in both exposure groups, a rate of 1.8% did not appear to be greater than that which might be expected in similar unexposed workers. The urinalysis showed no clear difference between the two exposure groups or any group tendency toward abnormality. Hematocrit index, lymphocyte count, SGOT and SGPT activities, and creatinine and BUN values were within the normal range. White blood cell counts were above the normal limit during the 4th, 8th, and 12th years of employment for the moderate-exposure group. The mean group values for monocyte cell count were within normal limits except for the employees with more than 6 years of moderate exposure, in whom values fluctuated fairly widely around the laboratory normal. The difference between the average values for the two exposure groups was statistically significant (t value was 4.35 at a P value of less than 0.05) at the 3rd year. Eosinophil cell count was slightly elevated for the moderate-exposure group during the 2nd and 5th years of epichlorohydrin exposure. Lactate dehydrogenase activity was elevated in both groups. Examination of pulmonary function data indicated that the mean values for both groups did not differ from their normal values. The

albumin-to-globulin ratio was normal for both groups, but, at the 4th year of exposure, the ratio for the moderate-exposure group was significantly lower (t value 3.88, with a P value of less than 0.05) than that of the minimal-exposure group. Based on all these findings, the consultants concluded that there were no toxic effects on the blood, liver, or kidneys related to the epichlorohydrin exposures.

This study, although helpful, is inadequate to fully estimate the health hazards associated with epichlorohydrin exposure for several reasons. The data base comprises a group of employees occupationally exposed to epichlorohydrin for periods of 6 months-16 years, but no consideration was given to those who dropped out because of illness, retirement, or death. There is no way to evaluate from this study the importance of the group lost from the observation. A major deficiency of this study is the lack of a control group. In the absence of such a group, the "normal" range of the clinical and the biochemical tests is dependent on laboratory values alone. Further, because of the lack of controls, the consultants compared the effects of the moderate-exposure group with those of the minimal-exposure group. The consultants stated that the measure of exposure was "a crude one" and that it was only an estimate by the company of whether a given individual's exposure was minimal or moderate. No quantitative data with regard to exposure were provided, and there is no indication of even what range of concentration was referred to by the classifications "moderate" and "minimal." Therefore, any absence of dose-related effects could be accounted for both by the absence of a clear distinction between the groups and by loss of an affected segment of population. From the biochemical data, it is possible to conclude that

groups of individuals "exposed" to epichlorohydrin do not show variations from the measured norms held to be appropriate by the laboratory. Further, because of the deficiencies discussed in this paragraph, the significance of the finding on respiratory tract illness is dubious. If the number of tests in any year of employment was related to the number of employees, the length of employment in the moderate-exposure group was much shorter than in the minimal-exposure group, ie, less than half the workers were still employed during the 1st year and available for tests. In the minimal-exposure group, this point was reached in the 2nd year. The absence of mortality data further limits the usefulness of the study for detecting any chronic effects such as cancer. Animal studies [39-41] have indicated that epichlorohydrin induces sterility in rats; yet, reproductive histories were not checked. In summary, the blood chemistry and liver and kidney functions in groups of individuals exposed to epichlorohydrin at unknown concentrations were not different from the company laboratory normal values.

Animal Toxicity

Animal studies provide useful models to confirm and to provide guidance in understanding the effects of epichlorohydrin on humans. Animal toxicity studies with epichlorohydrin have used different species of animals exposed at different concentrations for different exposure periods. [25-27,29-31,42-49] To facilitate comparison of the data, the total amount of epichlorohydrin inhaled has been calculated from the concentration of epichlorohydrin in the inhaled air and the duration of exposure by the equation of MacFarland. [50] The calculated amount of inhaled

epichlorohydrin is not equivalent to the total mass of epichlorohydrin absorbed by the experimental animal or subject for two reasons. First, the formula is based solely on respiratory considerations and does not include terms for other routes of exposure, such as oral and dermal. Secondly, experimental evidence with other low-molecular-weight lipophilic molecules indicates that less than 100% of the inhaled material will be adsorbed by the respiratory system. [50-54] Consequently, the amount of inhaled epichlorohydrin may be less than or greater than the true mass of epichlorohydrin absorbed by the entire organism. The minute volumes used in this document are 1.23 liter/minute/kg in mice, 0.61 liter/minute/kg in rats, and 0.25 liter/minute/kg in rabbits. [56,58] If the body weight of animals in the studies considered in this document differed from those used by Guyton [57] or Crosfill and Widdicombe, [56] the minute volume was estimated by linear extrapolation. The absolute values obtained are likely to be underestimates of the minute volume since the animals used by Guyton [57] were either resting or recovering from anesthesia, and the animals used by Crosfill and Widdicombe [56] were all anesthetized. In contrast, the epichlorohydrin-treated animals were generally free to move about and hence may have had increased minute volumes. Where the actual weights of the experimental animals were not stated, it is assumed that the mice weighed 0.02 kg and the rats, 0.25 kg. It is also assumed that the animals were placed in the inhalation chamber after a constant concentration of epichlorohydrin had been reached. Based on these assumptions, these calculations provide a crude estimate of the relative mass of epichlorohydrin inhaled via the pulmonary route by the different species.

In 1941, Freuder and Leake [25] investigated the effects of epichlorohydrin administered by various routes to several species of animals. Acute toxicity was determined by exposing white mice to epichlorohydrin vapor at concentrations of 2,370, 8,300, and 16,600 ppm for 30-60 minutes. The concentrations of epichlorohydrin were estimated from the air flowrate and the total weight of epichlorohydrin lost from the container. Irritation of the nose and eyes were observed, the effects being more severe at higher concentrations. All 30 mice exposed at 16,600 ppm for 30 minutes (approximately 2,315 mg/kg, inhaled amount) and all 20 mice exposed at 8,300 ppm for 30 minutes (equivalent to 1,158 mg/kg, inhaled amount) died. All 30 mice exposed at 2,370 ppm of epichlorohydrin for 60 minutes (approximately 661 mg/kg, inhaled amount) survived.

Ten white mice were exposed to epichlorohydrin vapor at 2,370 ppm for 60 minutes daily until all died. [25] Two animals died on the 3d day of administration, two more died on the 6th day, one on the 7th, two on the 8th, one on the 9th, and the last two on the 16th day. A similar sequence of signs was evident in all mice exposed to epichlorohydrin. Nose and eye irritations were followed by gradual cyanosis, muscular relaxation of the extremities, stiffening of the tail, and a fine body tremor. The respiration decreased markedly several hours before death and ceased completely before cardiac arrest. Terminal clonic convulsions occurred in some animals.

The effect of absorption of pure epichlorohydrin through the skin was investigated on rats and on guinea pigs. [25] A gauze wetted with epichlorohydrin was applied for 1 hour to a shaved abdominal area (about 1 sq cm) of each rat. A double layer of adhesive plastic was applied over

the gauze to hold it in place and to reduce evaporation. Local irritation and discoloration developed, followed by systemic signs of epichlorohydrin poisoning. The doses were estimated to be 2, 1, or 0.5 cc/kg. At 2 cc/kg, 18 of 20 rats died; at 1 cc/kg, 2 of 10 rats died; and, at 0.5 cc/kg, all 10 rats survived. Six of 10 rats survived three daily dermal applications of epichlorohydrin at 1 cc/kg, while four applications of epichlorohydrin at 0.5 cc/kg killed all 10 rats. All of three guinea pigs survived single and repeated dermal applications up to a cumulative dose of 52 millimoles/kg (4 cc/kg) of epichlorohydrin. Evaporation was probably not prevented completely, and the amount of epichlorohydrin absorbed was probably less than implied by the dose figures quoted.

Groups of 15 white mice each were also administered epichlorohydrin in gum arabic solution by stomach tube. [25] Epichlorohydrin at a single dose of 0.5 cc/kg killed all 15 mice, whereas one dose of 0.23 cc/kg induced no fatalities. The effects of daily oral administration of epichlorohydrin also were investigated in groups of 15 mice. A total of 21 repeated administrations at 0.08 cc/kg and 4 at 0.23 cc/kg were required to kill all the mice in the group. The authors stated that the typical signs described previously were again evident. Subcutaneous injections of 0.08, 0.16, or 0.23 cc/kg of epichlorohydrin in gum arabic solution were administered daily to 10 white mice until all the animals died. Daily administration of epichlorohydrin at a dose of 0.08 cc/kg for 21 days or at 0.23 cc/kg for 4 days was sufficient to kill all the mice in the group. Thus, regardless of the route of administration (oral or subcutaneous), similar lethal effects were observed at equal doses.

A transitory fall in blood pressure without any marked effect on respiration was observed in three cats and in two dogs, which had been anesthetized with pentobarbital and given single iv injections of epichlorohydrin at a dose of 0.1 millimole/kg (0.008 cc/kg). [27] The minimum lethal iv dose was determined to be about 1 millimole/kg (0.08 cc/kg) in cats and dogs. Death occurred within 2 hours of epichlorohydrin administration. Freuder and Leake [25] stated that deaths from exposure to epichlorohydrin in the animals were due to the effects on the CNS, especially on the respiratory center. They further stated that muscular paralysis and gradual depression of respiration sometimes preceded the respiratory and cardiac failure. The authors observed no microscopic changes in the lungs, heart, kidneys, spleen, or bowel. This report indicates that epichlorohydrin presents a hazard of systemic poisoning from skin absorption. It is noteworthy that the authors did not examine the liver or observe kidney damage.

In 1949, Carpenter et al [58] reported the effect of inhalation of epichlorohydrin on rats as a part of a toxicity range-finding study in which the results were given only in ranges rather than in specific figures. Inhalation of epichlorohydrin at 250 ppm for 4 hours killed two, three, or four of six rats. The authors rated epichlorohydrin as definitely hazardous.

In 1959, Gage [26] exposed five groups of eight albino Wistar rats each (four males and four females) to epichlorohydrin vapor at 120, 56, 27, 17, and 9 ppm. Use of control animals was not reported. The vapor was generated by atomizing epichlorohydrin in propanol solution into a metered stream of air. The concentration of epichlorohydrin was calculated from

the internal diameter of the feed syringe, the rate of piston movement, and the airflow. The concentration was also determined colorimetrically each day. All animals were exposed for 6 hours/day, 5 days/week, for 11-19 exposures. All rats [26] inhaling epichlorohydrin at a concentration of 120 ppm for 11 exposures (approximately 1,132 mg/kg, total amount inhaled) experienced labored breathing, profuse nasal discharge, a marked loss in weight, and leukocytosis. Urinary protein excretion was "more than double the normal value," which suggests damage especially to the kidneys. Microscopic examination of the kidneys showed areas of leukocytic infiltration in all rats and atrophy of the peripheral cortical tubules in four of the eight rats. Microscopic examination of the liver revealed general congestion which was accompanied in one case by areas of necrosis. Lung congestion, edema, consolidation, and inflamed areas with signs of abscess formation were also observed. Although epichlorohydrin is the most plausible causative agent, the absence of controls exposed to the propanol vehicle alone makes it difficult to attribute these changes solely to epichlorohydrin.

The rats exposed to epichlorohydrin at 56 ppm for 18 periods (approximately 864 mg/kg total amount inhaled) showed respiratory distress, nasal discharge, and weight loss. [28] Urinary protein excretion, hemoglobin concentrations in blood, and differential cell counts were normal. Microscopic examination showed only an abscess in one lung, which the author did not attribute to epichlorohydrin exposure.

Rats exposed to epichlorohydrin vapor at 27 ppm for 18 days (approximately 417 mg/kg total amount inhaled) showed mild nasal irritation. [28] The lung of one rat contained hemorrhagic and

consolidated areas. Rats exposed to epichlorohydrin at 17 ppm for 19 exposure periods showed no apparent effects at necropsy or on histopathologic examination. This exposure most likely resulted in an estimated inhaled amount of about 277 mg/kg. Two of eight rats developed pulmonary infections when exposed to epichlorohydrin at 9 ppm for 18 exposures (approximately 139 mg/kg, total amount inhaled); no effects were observed in the other six animals.

Gage [26] also exposed two groups of two rabbits each to epichlorohydrin vapor. The periods of exposure were not mentioned, but probably, like the rats, the rabbits were exposed 6 hours/day, 5 days/week. The first group was exposed for 20 daily periods at 35 ppm (approximately 439 mg/kg total amount inhaled). The second group was exposed for two periods at 16 ppm (approximately 20 mg/kg total amount inhaled). The latter exposure was reduced to 9 ppm and was continued for 20 more days (approximately 113 mg/kg total amount inhaled). Thus, the second group of rabbits is estimated to have inhaled a total amount of 133 mg/kg. Inhalation of epichlorohydrin at 35 or 16 ppm produced nasal irritation. At 9 ppm, no adverse effects were observed. Post-mortem examination did not reveal any abnormalities. Subsequent to these observations, Gage [26] recommended that the epichlorohydrin concentration in the occupational environment where employees are working continually without respiratory protection should not exceed 5 ppm. However, it is noted that Gage did not attempt to investigate any long-term effects of epichlorohydrin inhalation since the longest exposure lasted only 19 days. The recommendation of 5 ppm was therefore based only on effects resulting from short-term exposure.

In 1961, Kremneva and Tolgskaya [27] reported the effects of epichlorohydrin on mice, rats, and rabbits. Routes of administration were stomach intubation, subcutaneous injection, inhalation, and skin and eye application. Three groups of 10 mice and 5 rats each were administered aqueous solutions of epichlorohydrin by stomach tube in doses of 500, 325, and 250 mg/kg. All animals given doses of 500 or 325 mg/kg died within the first 2 days. In both rats and mice, the same type of intoxication pattern was evident: low mobility, slow and labored breathing, hyperemia of the skin, subcutaneous bleeding, ataxia, periodic body tremor, and distention of the abdomen. Microscopic examination of tissues of the dead animals revealed plethora of the internal organs, hemorrhage and edema of the lungs and pulmonary tissue, vacuolization of the liver cells with what was described as fatty degeneration, and degenerative processes in the epithelium of the convoluted tubules accompanied by some necrosis in the kidneys. Foci of necrosis in the stomach and intestinal mucosa also were observed. At the 250-mg/kg dose, no visible signs of intoxication were evident during the 14-day observation period.

A total of 50 mice were injected with epichlorohydrin at doses of 500, 375, 250, and 125 mg/kg. [29] The results of the injections were not described except that, at doses of 500 and 375 mg/kg, all of the mice died, and, at 250 mg/kg, 7 of 10 mice died. Epichlorohydrin at a dose of 125 mg/kg was tolerated without visible alteration in the behavior of the mice.

The skin-penetrating ability of epichlorohydrin was tested when the tails of mice (2 groups, 10 mice each) were lowered into test tubes containing pure epichlorohydrin. Six of ten mice died within 3 days from a single 1-hour exposure. All of the 10 mice in the second group subjected

to repeated 20-30 minute immersions died after 2 or 3 exposures. Morphologic examination of dead animals revealed congestion of the internal organs, edema, brain hemorrhage, and severe degenerative alterations or necrosis of the epithelium of the convoluted tubules of the kidneys. The authors [29] noted that the signs of intoxication in these mice were similar to those observed in animals injected subcutaneously with epichlorohydrin. Thus, the evidence indicates that epichlorohydrin can effectively penetrate the skin and induce severe systemic poisoning.

For inhalation exposures, 70 mice and 63 rats in groups of 10-18 each were placed in a 100-liter static chamber. [27] Epichlorohydrin was placed in the chamber and allowed to evaporate freely. Air was sampled from the chamber after 15-30 minutes and again 90 minutes after the start of the 2-hour exposure. The actual concentrations were determined by a method based on the reduction of chlorohydrins to chloride ions. Because of the static chamber, the measured concentrations at these times are not equal to either the average or the total exposure. Exposure to epichlorohydrin at concentrations ranging from 7.5 to 9.0 mg/liter (1,950-2,340 ppm) caused the death of all 10 animals of both species during the 1st day. There were no deaths in rats and mice exposed to epichlorohydrin at 0.9-1.2 mg/liter (approximately 234-312 ppm). Once again, it should be noted that the concentrations of epichlorohydrin reported give only an approximate index of exposure.

A group of 10 rats was exposed for 3 hours daily to epichlorohydrin vapor at 0.02-0.06 mg/liter (5.2-15.6 ppm) for up to 6.5 months. [27] No deaths or signs of intoxication were observed. The gain in body weight lagged behind that of the controls. The threshold of excitability of the

nervous system increased in the exposed animals during months 2-5, but returned to the preexposure value by the 6th month. The blood pressure of the intoxicated animals fluctuated around a normal value of 95-100 mmHg, in contrast to the normal 90-95 mmHg. Oxygen consumption by the exposed animals increased during the first 2 months but decreased after 5-6 months. No significant variations were observed in the composition of the peripheral blood. Pathomorphologic study revealed an occasional, slight thickening of the alveolar septa and catarrhal bronchitis. Degenerative alterations in the liver and kidneys were insignificant. The authors [29] concluded that, in rats, concentrations of 0.02-0.06 mg/liter (approximately 5.2-15.6 ppm) approximated the threshold. Although the authors did not define threshold, it is interpreted to mean the concentration at which no measurable adverse effect would occur in rats.

Kremneva and Tolgskaya [27] also studied the effects of epichlorohydrin on the mucous membranes of the eyes. A drop of epichlorohydrin placed into the conjunctival sac of a rabbit's eye caused blepharospasm, hyperemia of the mucous membrane, lacrimation, pupillary constriction, reduction of the eye slit, clouding of the cornea, and edema of the lids. Recovery occurred within 10 days. The persistent skin damage following dermal contact with epichlorohydrin seen in humans [35] is confirmed by these animal studies. The suggestion of Kremneva and Tolgskaya [27] that measures be taken to provide skin and eye protection to avoid damage is supported by others. [11,19,25,35,37]

Based on these extensive studies, Kremneva and Tolgskaya [27] suggested 0.001 mg/liter (approximately 0.26 ppm) as a tentative maximum permissible concentration of epichlorohydrin in the occupational

environment. Bartlett [59] reported the pulmonary ventilation rate as a function of the degree of the metabolic activity which ranged from sleep to maximum work. A ventilation rate of 25 liters/minute or 1.5 cu m/hour is intermediate between light and medium work. Consequently, this ventilation rate is an estimation of a spectrum of work activities in the manufacture, use, and handling of epichlorohydrin. For an individual working 10 hours/day with a ventilation rate of 25 liters/minute or 1.5 cu m/hour, the approximate amount inhaled during an 8-hour workday would be 0.21 mg/kg for a 70-kg man.

In 1967, Pallade et al [29] found the subcutaneous LD50 of epichlorohydrin in rats to be 150 mg/kg. An 8% epichlorohydrin solution in propylene glycol was used and the animals were observed for 2 weeks. Application of 0.5 ml of epichlorohydrin to the skin of an unspecified number of rabbits for 24 hours caused a lesion with a central zone of coagulation necrosis surrounded by one of a hard edema involving the superficial layer of the dermis. A zone of erythema with punctiform hemorrhages extending beyond the area of contact with epichlorohydrin appeared at the periphery. In all cases, the areas of necrosis and erythema became covered with a bloody fibrinous scab after 2-3 days that persisted for up to 30 days. Application of 0.1-0.2 ml of epichlorohydrin for 24 hours caused similar, but less severe and smaller, lesions. The authors reported that all rabbits on both application schedules recovered.

Effects of epichlorohydrin [29] by the cutaneous route were determined by immersing the tails of 10 mice for 15-20 minutes in test tubes containing undiluted epichlorohydrin. [29] Seven of the mice died, and the three survivors showed local lesions leading to the loss of the

distal portion of the tail.

Effects on the kidneys were studied in 57 rats divided into four groups. Epichlorohydrin was administered by an unspecified route in single doses of 180, 150, 125, and 100 mg/kg. [29] The animals were placed in metabolism cages for a period of 2 weeks. Daily urine outputs were examined for albumin concentration and sediment. Methods of analysis were not reported. At 100 mg/kg, 22 of 27 rats (81.5%) had oliguria, and one (3.7%) had anuria. Anuria was observed at 125 mg/kg in 7 of 12 rats, (58.3%) and, at 150 mg/kg, in 10 of 12 rats (83.3%). Following the administration of epichlorohydrin at 125 or 150 mg/kg, the rest of the animals had oliguria. At a dose of 180 mg/kg all six (100%) animals had anuria. Mortality rate was 66.7% for animals receiving 180 or 150 mg/kg epichlorohydrin. Mortality rates were 50 and 7.4%, respectively, in the 125 mg/kg and the 100 mg/kg groups.

Epichlorohydrin at a single dose of 150 mg/kg was injected by an unspecified route into 80 rats. [29] Blood catalase (Enzyme Commission Number, E.C. 1.11.1.6) and carbonic anhydrase (E.C. 4.2.1.1) activities were determined in 55 and 25 animals, respectively, on days 1, 3, 5, 7, 9, and 16 after injection. Blood catalase and carbonic anhydrase activities were measured in 26 and 12 untreated control rats, respectively. The catalase activity of the treated animals at the end of the 16-day period showed a statistically significant decrease of 20% (P value equal to or less than 0.05) in contrast to the 2.5% decrease observed in control rats. Decreases in carbonic anhydrase activity of about 10% also were observed in the treated animals. The long duration of these effects on enzyme activities is noteworthy, and, as the authors pointed out, this persistence

suggests irreversible, and perhaps cumulative, changes.

For microscopic studies, [29] 23 rats were treated with epichlorohydrin at 150 mg/kg, and 14 rats were treated at 180 mg/kg. A similar, or probably the same, study was reported in greater detail in Rumania by Rotaru and Pallade, [30] who reported administering 150 or 180 mg/kg of epichlorohydrin by single subcutaneous injections to 23 and 14 albino rats, respectively. Tissues from animals killed at 24 or 48 hours, or 5 or 10 days after the injection and from those which expired during the experiment were examined microscopically. Immediately after death, samples from the myocardium, lungs, liver, kidneys, spleen, stomach, intestine, adrenals, and brain were taken for study. The induced effects were similar at both doses, but were more severe at the higher dose. The kidneys were the most damaged organs. Animals examined at 24 hours showed ischemia of the cortex and congestion of the deep cortical layers near the medulla. Various degrees of congestion and interstitial edema with hemorrhagic foci also were present in the medulla. In all cases, prevailing lesions of degenerative or necrotic nature were evident in all nephrons but were especially severe in the proximal parts of the nephrons. Diffuse, cloudy intumescences, granular alterations, granular vacuoles, and homogeneous eosinophilic coagulation also were observed. The authors attributed these observations to a marked cellular metabolic imbalance. The epithelium was severely affected and showed nuclear damage, as evidenced by karyolysis, karyorrhexis, and karyopyknosis. This damage was attributed by the authors to the irreversible nature of the degenerative lesions which became necrotic. Examination of the tubular basal membranes revealed that, in some cases, they were discontinuous for various lengths, and that

disruptive cortical lesions were especially prevalent. Minimal perinecrotic inflammatory infiltrates appeared 48 hours after treatment at both doses. On the 5th day, epithelia with hypertrophic nuclei in the necrotic zones and occasional binuclear regeneration were present. On the 10th day, most of the tubules consisted of regenerated epithelium, and the ischemic necrotic zones were no longer recognizable. In general, the gross and microscopic tissue damage detected during the first 48 hours was no longer present, despite the persistence of changes in the activity of blood enzymes. The signs observed in the animals as a result of epichlorohydrin exposure appear to be those caused by a general systemic poison. The authors concluded that epichlorohydrin had a marked primary nephrotoxic action complicated by its action on the vascular system. They further concluded that regeneration could reestablish the structural integrity of nephrons in the surviving animals. However, the evidence is insufficient to conclude that the functional activity of the nephrons was fully restored.

Examination of other organs revealed generalized damage. [30] Alvèolar septal congestion, desquamative bronchial catarrh, and sporadic edema of the peribronchovascular connective tissue were detected in the lungs. The spleen exhibited frequent areas of sludged blood and small hemorrhagic foci. The stomach and intestine showed occasional slight congestion and edema in the mucosa with eventual desquamative catarrh. The liver and heart exhibited no appreciable microscopic alterations, and only a slight degree of congestion was present in the brain and adrenal glands.

In 1967, Soloimskaya [42] reported the effects of single subcutaneous injections of 125, 250, or 500 mg/kg of epichlorohydrin in 112 rats. For

controls, 93 untreated animals were used. Two days later, the blood of the rats injected with epichlorohydrin was examined for pyruvic acid, oxalacetic acid, and total citric and isocitric acids. Free aromatic amines were determined for animals treated at all three doses. At 250 mg/kg, increases in pyruvic acid, total citric and isocitric acids were observed, and at all three doses, increases in the free aromatic amine concentrations occurred in the blood. The concentration of oxalacetic acid in the blood decreased in animals given 250 mg/kg. Elevated concentrations of pyruvic acid and total citric and isocitric acids in the blood indicate altered rates of metabolism. After grinding the liver and incubating the mixture for 3 hours, its histaminase activity (E.C. 1.4.3.6) was determined. The average histaminase activity of the liver in 10 control animals was 130 ± 1.84 μg/g. Animals injected with a dose of 500 mg/kg of epichlorohydrin had a sharp decrease in histaminase activity to 42 ± 0.54 μg/g and those injected with epichlorohydrin at a dose of 250 mg/kg had a decrease to 83 ± 2.43 μg/g. In animals injected at a dose of 125 mg/kg, there was a decrease to 98 ± 1.56 μg/g. Thus, compared with the control animals, the rats at all three doses had sharply decreased histaminase activity in the liver. Although there is no evidence of decrease in histaminase activity in humans exposed to epichlorohydrin, the decrease in histaminase activity could be of clinical significance, particularly in people susceptible to allergies and sensitization. Other reports on the effects of epichlorohydrin on histaminase activity have not been found.

In 1972, Lawrence et al [31] reported on a series of experiments intended to determine acute and subacute effects of epichlorohydrin. The oral and ip LD50's for epichlorohydrin were determined by using unspecified

numbers of mice, rats, guinea pigs, and rabbits. The animals were observed for 7 days after epichlorohydrin administration. The ip LD50 ranged from 0.10 to 0.14 ml/kg for mice, rats, guinea pigs, and rabbits, while the oral LD50 was 0.20 ml/kg for mice and 0.22 ml/kg for rats. The dermal LD50 was 0.64 ml/kg for rabbits. Inhalation of epichlorohydrin vapor by mice resulted in an LT50 of 9.13 minutes at 71.89 mg/liter (18,690 ppm). The concentrations were not verified by analytical techniques. However, it should be noted that the animals were probably exposed to epichlorohydrin at an increasing concentration up to 71.89 mg/liter (18,690 ppm).

Tissue culture experiments were performed by the agar-overlay method with mouse fibroblasts. [31] Epichlorohydrin in cottonseed oil was applied to paper disks which were placed on the surface of the agar and incubated at 37 C for 24 hours. A cytotoxic response had occurred when a clear zone of lysed cells surrounded the disk. Epichlorohydrin at 0.00122% v/v (0.00016 M) was cytotoxic to the cells, but, at 0.000486% v/v (0.000062 M) or less, no effects were observed. The hemolytic activity of epichlorohydrin was evaluated by estimating the amount of hemoglobin released by addition of 0.2 ml of oxalated whole rabbit blood to 10 ml of various saline solutions of epichlorohydrin. When the epichlorohydrin concentration was 0.01 M, hemolysis was first detected; when it was 0.0375 M, 50% hemolysis occurred. In the absence of further experimental details, it is not possible to draw conclusions about the dose-response relationship for epichlorohydrin-induced hemolysis.

To assess the irritant effects on eyes, 0.1 ml of epichlorohydrin solution in cottonseed oil was instilled into the right eyes of the rabbits; the left eyes served as the untreated controls. [31] The eyes

were examined every 30 minutes for 3 hours. Corneal damage was present in 80% of the animals and a lesser degree of irritation occurred in the rest of the animals. Epichlorohydrin was found to be a strong ophthalmic irritant.

There was no evidence of sensitization to epichlorohydrin, as determined by the maximization test in 5 Hartley-strain guinea pigs. [31] Groups of 12 male Sprague-Dawley rats were injected ip daily for 30 consecutive days with 0.00955 or 0.01910 ml/kg of epichlorohydrin or 0.01910 ml/kg of cottonseed oil. At the end of 30 days, hemoglobin values were increased significantly at the low dose but decreased significantly at the higher dose (P values less than or equal to 0.05). The concentration of neutrophilic metamyelocytes increased significantly (P value less than or equal to 0.05) in the high-dose group but remained equal to that of controls for the rats administered epichlorohydrin at the lower dose. Lymphocytes showed an insignificant dose-related decrease in frequency. A slight, insignificant dose-related increase in clotting time was also observed. Hepatic function, as measured by the BSP test, was not impaired. The heart-to-body weight ratio increased in a dose-related way but the increases were not statistically significant. The ratio of the weight of the kidney to body weight increased significantly with both doses (P value less than or equal to 0.05). The ratio of brain-to-body weight of the rats was higher in the epichlorohydrin-treated rats than in the controls. Microscopic examination did not reveal changes in any organs except in the lungs. Lesions in the lungs were evident in all groups, but the incidence and severity were "somewhat greater" in the treated animals than in the controls. It is noteworthy that the authors did not detect any kidney

damage in the microscopic examination.

Lawrence et al [31] also investigated the effect of administering epichlorohydrin ip to rats on Mondays, Wednesdays, and Fridays for 12 weeks. Four groups of male Sprague-Dawley rats received either 0.04774 ml/kg of cottonseed oil (control) or 0.0095, 0.0190, or 0.04774 ml/kg (1/10, 1/5, and 1/2 the ip LD50) of epichlorohydrin in cottonseed oil. The number of animals in each group was not specified. A significant reduction (P value less than or equal to 0.01) in the body weight gain accompanied by reduced food intake was seen in the group receiving epichlorohydrin at the highest dose. A dose-related (the higher the dose, the greater the reduction) and statistically significant (P less than or equal to 0.05) decrease in hemoglobin was observed. All animals treated with epichlorohydrin had lower hematocrit and erythrocyte counts than the control rats, but this was significant (P value less than or equal to 0.05) only for the hematocrit value of the middle-dose group. An increase in the concentration of platelets in the blood also was observed in the epichlorohydrin-treated animals. Total leukocyte counts were lower in the low-dose group and higher in the highest-dose group than in the control group. These differences were not significant (P value less than or equal to 0.05). Leukocyte counts for the middle-dose and control groups were the same. A dose-related increase in the average percentage of segmented neutrophils was observed but was significant (P value less than or equal to 0.01) only for the high-dose group. The percentage of eosinophils increased in all experimental groups, the increases in the low- and the high-dose groups being significant (P value less than or equal to 0.05). Significant reductions in the percentage of lymphocyte in the total

leukocyte count were observed in the animals treated with the two highest doses (P values less than or equal to 0.05 and 0.01, respectively). The ratio of the weight of the brain to that of the body was significantly lower (P value less than or equal to 0.01) in the animals treated with epichlorohydrin at the highest dose than in the control animals; this is in contrast to the effect obtained in animals receiving 30 daily doses of epichlorohydrin. The change in the brain-to-body weight ratio suggests abnormal changes in the CNS. The organ weight-to-body weight ratios for heart, kidneys, and liver were significantly (P values less than or equal to 0.01, 0.01, and 0.05) higher for the animals treated with the highest dose than for the controls. The ratio of spleen-to-body weight was not significantly different from that found in the controls. The results indicate that repeated doses induce a cumulative effect on basic cellular growth with a subsequent perturbation of the normal rates of growth of these internal organs.

The effect of epichlorohydrin on pentobarbital-induced sleeping time was studied in mice. [31] Male ICR-strain mice in groups of 10 were administered 1/10, 1/5, or 1/2 of the acute ip LD50 dose (0.14 ml/kg) of epichlorohydrin. Control mice were administered ip saline injections. Similar groups of mice were exposed to epichlorohydrin vapor at 1/10, 1/5, or 1/2 of the LT50 dose (71.89 mg/liter, 9.13 minutes). Control mice were placed in an inhalation chamber and were exposed to uncontaminated air. Twenty-four hours after exposure to epichlorohydrin by either route, 50 mg/kg of sodium pentobarbital was administered ip. A dose-related increase in sleeping time was observed in all the epichlorohydrin-treated animals; however, the only significant increases (P value less than or equal to

0.01) were in the groups receiving the highest ip dose or the highest inhalation exposure. Based on these extensive studies, it can be concluded that epichlorohydrin is severely irritating to the skin and the eyes, and perhaps to the lungs. Further, it also affects some metabolic processes of the liver. In most cases, the severity of its effects appears to be dose dependent.

In 1972, Lawrence and Autian [44] further examined the effect of epichlorohydrin on pentobarbital-induced sleeping time. Groups of 10 male ICR mice were exposed to epichlorohydrin vapor at 98.20 mg/liter (approximately 25,500 ppm) for 0.92, 1.83, or 4.58 minutes daily for 3 days (0.1, 0.2, or 0.5 times the inhalation LT50). Based on the assumptions discussed at the beginning of this section, the approximate amounts inhaled were 333, 663, and 1,600 mg/kg, respectively. Pentobarbital-induced sleeping time was measured 24 hours after the last exposure. Compared with that of the control animals, an increased sleeping time was apparent in the test rats, suggesting an effect on microsomal processing enzyme systems of the liver.

Fomin [28] exposed three groups of 15 male albino rats to epichlorohydrin vapor for periods of 24 hours/day for 98 days at 20 ± 0.026, 2 ± 0.007, or 0.2 ± 0.001 mg/cu m. These concentrations approximate 5.2 ± 0.01, 0.5 ± 0.002, or 0.05 ± 0.0003 ppm and the total amounts inhaled are estimated to be 1,722, 172, or 17 mg/kg, respectively. Epichlorohydrin concentrations were determined colorimetrically. A fourth group of 15 animals served as a control. Peripheral blood was sampled for analysis of fluorescence of leukocytes from five rats in every group, at first once a week and then once every 2 weeks. Compared with the controls, animals

receiving epichlorohydrin at the highest dose had a sevenfold increase in the number of leukocytes with altered fluorescence. The nucleic acid concentration in the blood of the same animals decreased to 90.73 mg% in contrast to 127.07 mg% in the control group. An increase in the amount of urinary coproporphyrin, 2.68 μg compared with 1.07 μg in the control group, occurred in the animals receiving epichlorohydrin at the highest dose. Reduced weight gains and prolonged latent periods of the motor defense reaction were also observed in this group of animals. Gross and microscopic examinations disclosed emphysema, bronchopneumonia, edematous areas, and loosening and swelling of the adventitia of blood vessels in the lungs. Cloudy swelling of the epithelium of the convoluted tubules in the kidneys and foci of interstitial hemorrhage and venous congestion in the heart were evident. Severe lesions of the neurons in the medulla oblongata, Ammon's horn, and cerebellum were also present.

Animals inhaling epichlorohydrin at 0.5 ppm showed an increase in leukocytes with altered fluorescence, a decrease in the nucleic acid content of the blood, but no significant effects on the amount of urinary coproporphyrin. [28] The concentration of leukocytes with altered fluorescence increased significantly (95% probability of not being a variation by chance), but the effect was less marked than on the animals treated at the highest dose. Animals in the third group, inhaling epichlorohydrin at 0.05 ppm, did not show similar effects. There were no morphologic differences between the control animals and those in the last two groups.

Based on the results of this continuous inhalation study, Fomin [28] recommended that the mean diurnal maximum permissible concentration of

epichlorohydrin in the atmosphere not exceed 0.2 mg/cu m (approximately 0.05 ppm). The exposure in this study was continuous and the effect of intermittent recovery periods was not evaluated.

In 1969, Golubev [45] recorded changes in the diameters of the pupils of the eyes of rabbits. Groups of six rabbits were used to ascertain the irritating effects of eight different chemicals, including epichlorohydrin. The rabbits' eyes were illuminated with a uniform reflected light, and the diameters of the pupils were measured with an instrument referred to as a tangential pupilometer. A 0.25 M solution of epichlorohydrin was instilled into the conjunctival sacs and the pupil diameters were measured 1, 3, 5, 10, 15, 20, 25, and 30 minutes later. In the control rabbits, the pupil diameters were measured both before instillation and at similar time intervals after instillation of 0.05 ml of saline solution into the conjunctival sacs. Epichlorohydrin caused constriction ranging from 1 to 16% during the first 20 minutes, the initial diameter being considered 100%. The author noted that this effect was elicited at an epichlorohydrin concentration that caused no visible changes in the conjunctivae or cornea. Thus, epichlorohydrin at 0.25 M (2.3%) has a measurable effect on the eyes.

In 1968, Pallade et al [46] subcutaneously injected 67 white rats with a single dose of epichlorohydrin at 125 mg/kg to investigate epichlorohydrin-induced kidney damage. Prior to injection, the urine of each animal was examined for protein, potassium, and sodium; thus, each animal served as its own control. The animals were kept in metabolism cages; their urines were examined 1, 2, 3, and 8 days after epichlorohydrin administration. Oliguria or anuria was exhibited by 53 (79%) animals and polyuria by 4 (6%). The remaining 10 (15%) produced urine at normal rates.

Of the 53 rats that produced little or no urine during the period immediately after the administration of epichlorohydrin, 7 (13.2%) entered a stage of polyuria within 2-3 days after the administration of the dose. The mortality rate was 13.4%, death occurring only among the oliguric and anuric animals. Urinary protein was determined by spectrophotometry and urinary potassium and sodium were measured by flame photometry. Although it was evident in all animals, proteinuria was more marked in the oliguric animals. The excretion of protein in the urine returned to normal after 8 days. Sodium concentration in the urine was low and remained so even after 8 days; the potassium concentration was elevated initially but returned to normal within 8 days.

Serum was examined 48 hours after epichlorohydrin was administered to 60 rats. [46] Protein concentrations were determined by a modified Weichselbaum method, sodium and potassium by flame photometry, and serum lipids by microphotometry. Reductions in serum protein and sodium concentrations and an elevation in the serum potassium concentration were observed. The concentrations of total serum lipids and the lipase activity of serum were not different from those in 40 untreated rats serving as controls.

Pallade et al [46] noted that proteinuria and the parallel oliguric and anuric conditions indicated the occurrence of renal damage. If tissue repair and regeneration had occurred, the animals survived. They concluded that the signs of renal disorders confirmed that epichlorohydrin is nephrotoxic to rats. Therefore, medical examinations oriented to the detection of renal disorders were recommended for workers exposed to epichlorohydrin.

In 1966, Shumskaya and Karamzina [47] used epichlorohydrin as a known nephrotoxin to evaluate various measures of kidney function in rats. Since the intent of these investigations was not to identify epichlorohydrin toxicity, details such as time of exposure and number of animals used were generally not specified. Polyuria, secretion of urine of low specific gravity, proteinuria, reduced urinary chloride concentrations, and increased concentrations of nitrogen-containing substances in the urine were found.

In 1971, Shumskaya et al [32] conducted another study similar to the one discussed in the previous paragraph. [47] Experiments with single 4-hour inhalations of epichlorohydrin at 0.35 mg/liter (91 ppm), at 0.02 mg/liter (5.2 ppm), and at 0.007 mg/liter (1.8 ppm) were conducted on three groups of 60 male white rats each; the control group comprised 60 rats. Information on how epichlorohydrin vapor was generated and information on the size of the chamber were not provided. Neither was it indicated whether the chamber was operated in the static or the dynamic mode. The total amounts of epichlorohydrin inhaled during each of the 4-hour exposure periods are estimated to have been approximately 51, 2.9, and 1.0 mg/kg, respectively. The same effects seen in the previous experiment [47] were observed. In addition, the weights of the liver and kidneys were increased, whereas those of the lungs and the spleen were decreased. Removal of BSP from blood was decreased on the day of exposure, but not reliably on the day after the exposure. The production of urine was increased by all three levels of exposure, with concomitant decreases in the specific gravity of the urine. The daily output of chlorides in the urine on the day after exposure was usually increased by a larger factor

than the production of urine. The daily excretion of protein in the urine was also increased, but less than that of chlorides. No additional studies of pulmonary and splenic function were reported. Reductions in both oxygen consumption and body temperature also were observed. A significant (P value not given) stimulating influence on the mobility of spermatozoa also occurred in animals exposed to epichlorohydrin at the two lower concentrations. Even though the intent of these experiments was to evaluate various tests as indices of intoxication, important information on the toxicity of epichlorohydrin was generated. The results are summarized in Table XIII-2. They demonstrate that even short-term exposure to epichlorohydrin at approximately 1.8 ppm induces perturbations in basic physiologic processes such as consumption of oxygen and regulation of body temperature in mammals. These experiments [32,47] suggest that epichlorohydrin affects the function of the liver, as indicated by the BSP tests, and the kidney, as indicated by the production of urine and the reabsorption and filtration of chloride and protein. Lungs and spleen were also affected, but no assessment of the impacts on the functions of these organs was made. The authors concluded that epichlorohydrin affects the kidneys, liver, lungs, and nervous system.

Since a number of enzymes are involved in reabsorption and tubular secretion in the kidneys, Pallade et al [48] investigated the effects of epichlorohydrin on the activity of several enzymes. White rats of both sexes were administered epichlorohydrin subcutaneously at single doses of 125 mg/kg dissolved in propylene glycol. Animals were killed 2.5 or 24 hours after the administration of the dose and examined for various enzyme activities in the urine, renal tissue, and serum. Cytochrome oxidase (E.C.

1.9.3.1), succinic dehydrogenase (E.C. 1.3.99.1), and carbonic anhydrase (E.C. 4.2.1.1) activities were determined by manometric methods. Alkaline phosphatase (E.C. 3.1.3.1) activity was determined by the Gomori method, the transaminases activity by a colorimetric method, and catalase (E.C. 1.11.1.6) activity by an iodometric method.

Renal cytochrome oxidase activity was determined in 14 rats and in 10 controls 24 hours after they had been injected with epichlorohydrin. [48] Statistically significant (P value less than or equal to 0.01) inhibitions were observed in treated animals. Renal succinic dehydrogenase activity, determined 24 hours after epichlorohydrin administration, was similar for 10 experimental and 6 control animals. Examination of 40 treated and 30 control rats showed reductions in renal carbonic anhydrase activity of 6-11% 24 hours after the administration of epichlorohydrin. This reduction was not statistically significant. Glutamic-pyruvic transaminase (GPT) (E.C. 2.6.1.2) activity was measured 2.5 and 24 hours after administration in both renal tissue and serum. There were 30 animals in the group examined at 2.5 hours after epichlorohydrin administration and 40 in the group examined 24 hours postdose. At 2.5 hours, no change was observed in the kidneys, but a statistically significant (P value less than or equal to 0.01) increase in SGPT activity was observed at both the 2.5-hour and the 24-hour intervals. A significant reduction (P value less than or equal to 0.01) was observed at 24 hours; there were 0.230 units of activity in the controls in contrast to 0.100 units in the experimental group. The average SGPT activity in the experimental group ranged from 0.051 ± 0.022 units at 2.5 hours to 0.058 ± 0.018 units at 24 hours, in contrast to the control group average of 0.034 ± 0.010 units. Glutamic-oxaloacetic transaminase

(GOT; E.C. 2.6.1.1) activities in the kidney were similar for the controls and the intoxicated animals at 2.5 hours, but significantly (P values less than or equal to 0.01) different at 24 hours in the experimental rats (0.261 ± 0.046 units) versus 0.302 ± 0.040 units in the controls. SGOT activity was significantly increased in the experimental rats, 0.045 ± 0.009 units at 2.5 hours (P value less than or equal to 0.02) and 0.046 ± 0.010 units at 24 hours, (P value less than or equal to 0.01) in contrast to 0.040 ± 0.008 units observed in the controls. Alkaline phosphatase activity was assayed in 30 experimental animals and in 30 controls. The animals given epichlorohydrin showed a significant reduction (P value less than or equal to 0.01) in the mean kidney phosphatase activities (0.029 ± 0.008 units) at 2.5 hours but had a mean alkaline phosphatase activity comparable with that in the controls (0.033 ± 0.014 units) at 24 hours. However, serum alkaline phosphatase activity decreased progressively at both 2.5 and 24 hours. Catalase (E.C. 1.11.1.6) activity was measured in the kidneys and in the urine of 20 treated and 20 control animals. Renal catalase activity was only 3.93 ± 1.86 units in the experimental animals, whereas it was 7.91 ± 2.67 units in the controls. The average of urinary catalase activity of the epichlorohydrin-treated animals was about nine times that of the controls.

Pallade et al [48] stated that the observed changes in serum, urine, and kidney enzyme activities resulted from renal lesions or were consequences of general toxic effects in other tissues. In view of the reports on the nephrotoxicity of epichlorohydrin, [32,46,47] it seems likely that the altered serum enzyme activities may be due to renal lesions. As the authors [48] noted, however, damage to such other tissues

as liver and heart also can cause elevated blood enzyme activities. This study does not rule out the possibility that such effects are involved in the genesis of the observed changes in the enzymes of serum. In addition, direct chemical inhibition of enzyme-active centers or alteration of the rates of production or degradation of the enzyme could have caused the effects noted, but this was not discussed or evaluated by the authors. In particular, catalase, an enzyme participating in cellular oxidation-reduction reactions, is distributed widely in renal and hepatic cells and in erythrocytes. The reduced renal catalase activity observed may be attributed to renal damage, but, as the authors pointed out, the observed increase in urinary catalase activity could have been due to the presence of erythrocytes, leukocytes, or bacterial contamination as well as to leakage from damaged renal epithelial cells. Increases in serum transaminase activities (SGOT and SGPT), accompanied by reductions in these activities in the kidneys of experimental animals, were attributed by the authors to cellular lesions or to changes in mitochondrial permeability which precede cell destruction. The results of this study clearly indicate that exposure to epichlorohydrin induces major changes in several basic biochemical functions of the kidneys in laboratory mammals. The observed increase in urinary catalase activity suggests that examination of this activity may be a useful test to monitor for acute overexposure to epichlorohydrin in humans.

Grigorowa et al [60] determined the LC50 of epichlorohydrin in albino rats weighing 230-270 g and in albino mice weighing 18-26 g. Groups of 20 animals of each species were exposed to epichlorohydrin at concentrations of 0.190, 0.390, 0.855, 0.915, or 1.680 mg/liter (49.4, 101.4, 222.3,

237.9, or 436.8 ppm, respectively) for 4 hours in the case of the rats and for 2 hours in the case of the mice. One-half the animals in each group were subsequently exposed for 45 minutes to an environmental temperature of 35 C and a relative humidity of 35-50%. Survivors were counted 72 hours after exposure. The exposure to heat had no appreciable effect on the LC50. The values with and without heat were 2.2 and 2.4 mg/liter (582 and 635 ppm) for rats and 4.0 and 3.0 mg/liter (1,060 and 793 ppm) for mice.

Grigorowa et al [60] further exposed 2 groups of 60 male albino rats weighing 230-270 g to epichlorohydrin at concentrations of 0.6 or 0.06 mg/liter for 4 hours/day for 8 days. An additional group of 60 rats served as controls. One-half the animals in each group had a 45-minute exposure to an environmental temperature of 35 C and a relative humidity of 35-50% after each epichlorohydrin exposure; the other half received no temperature stress. Ten rats in each subgroup were killed on days 2, 4, or 11 of the experiment. Exposure at 35 C for 45 minutes on each of 8 days within an 11-day period had no effect on body weight. Inhalation exposure at a concentration of 0.6 mg/liter of epichlorohydrin for 4 hours/day for eight times during 11 days decreased body weight by about 9%. Combination of these two exposures, that to heat following immediately after that to epichlorohydrin, had the same effect on body weight as exposure to the chemical alone. This finding agrees with that relating to the LC50. In conclusion, the amount of heat stress had no effect on these two responses of rodents to epichlorohydrin.

Despite these two negative findings, there were a few instances in which addition of heat stress seemed to modify toxic actions by the chemical stressor. Thus, rats exposed to both heat and epichlorohydrin

were reported to have had somewhat less marked alterations of the structure of the liver and the thyroid follicles, but more pronounced ones of the adrenal medulla, than those exposed to epichlorohydrin alone. Five rats showed moderate accumulations, resembling abscesses in some instances, of leukocytes around blood vessels in the interstitial tissue of the thyroid. The animals tended to have increased relative weights of lungs, liver, kidneys, and adrenals (though not for each organ at all times of slaughter) and increased whole blood catalase (E.C. 1.11.1.6) and serum lactate dehydrogenase (E.C. 1.1.1.27) activities. Urinary volume and protein concentration decreased; changes in serum sodium, potassium, and leucine aminopeptidase (E.C. 3.4.1.1) were inconsistent. At the 0.06 mg/liter epichlorohydrin exposure, fewer effects from the addition of heat stress were observed and consisted principally of increases in the whole-blood catalase and serum leucine aminopeptidase activities. Therefore, exposure to an elevated environmental temperature sometimes altered some effects of epichlorohydrin exposure, most notably increasing the blood-catalase activity.

Effects on Reproduction

Epichlorohydrin-induced sterility has been reported in animals. [39-41] Cooper et al [39] administered epichlorohydrin suspended in arachis oil orally to adult male Wistar rats. No controls were used. Five daily doses of 20 mg/kg (a total of 100 mg/kg), or of 50 mg/kg (a total of 250 mg/kg), or a single dose of 100 mg/kg were given to five animals at each level. Animals receiving 5 daily doses of 20 mg/kg lost fertility during the first 2 weeks, but completely regained it by the third week. The

fertility of these rats was tested for 10 weeks. The sperm cycle in rats is 8 weeks. Rats receiving the five 50 mg/kg of epichlorohydrin doses were rendered completely sterile throughout a 10-week period. Microscopic examinations of reproductive tissues were done weekly for 20 consecutive weeks after the 100 mg/kg dose. Sterility occurred within the 1st week after treatment with epichlorohydrin at a dose of 100 mg/kg. Fertility returned during the 2d week, but the average litter size was reduced by about one-third. By 12 weeks, probable permanent sterility had occurred. Apart from small spermatoceles in the efferent ductules of the testes, histologic examination revealed no abnormalities up to 8 weeks after the administration of epichlorohydrin at a dose of 100 mg/kg. However, by 12 weeks, large retention cysts were present in the efferent ductules and the proximal caput in four of five sterile animals. Therefore, when the 100 mg/kg dose is administered in five equal daily doses, a reversible functional sterility occurs, while at a single dose of 100 mg/kg, spermatoceles form and permanent sterility may result.

Jones et al [40] investigated the antifertility effects of epichlorohydrin on Wistar rats. A single oral or ip administration of epichlorohydrin at a dose of 50 mg/kg in an aqueous solution produced "antifertility effects resembling those due to alpha-chlorhydrin." Details about measurement of antifertility, duration of the sterility, the time between dosage and onset of sterility, and the number of animals used were not reported.

In 1970, Hahn [41] gave daily oral doses of 15 mg/kg of epichlorohydrin for 12 days (a total of 180 mg/kg) to adult male rats of demonstrated fertility. Control animals were also observed. Two preestrus

female rats were placed in the cage of each male at different times during the study. After 7 days, the fertility of each male was evaluated on the basis of the number of uterine implantations in the females. Within 1 week, the males became infertile, but fertility was restored within the next week. On the 12th day, histologic examination of the testes, epididymis, prostate, and seminal vesicles showed no differences between the experimental and the control animals. The number of experimental animals was not reported. The kinetics of the effect cannot be evaluated since sterility observed at week 1 could have occurred on the 1st or the 7th day. Thus, the inference may be made that the sterility induced in male rats by epichlorohydrin is dose and time dependent. [39,41]

In 1972, Epstein et al [61] reported the effects of epichlorohydrin on the rate of pregnancy in ICR/Ha Swiss mice in a dominant lethal assay. A dose of 150 mg/kg of epichlorohydrin was administered to 10 male mice by ip injection. Each male was then caged with three undosed virgin female mice for 1 week. The females were replaced each week for 8 weeks and then killed and examined for pregnancy. The numbers of total live implants, early fetal deaths, and late fetal deaths were recorded. Since, in general, late fetal deaths were exceedingly rare, total implants and early fetal deaths were the only features of pregnancy analyzed. The authors did not report the observation of any effects of epichlorohydrin on early fetal deaths or other reproductive characteristics, including male fertility. Therefore, it can be concluded that epichlorohydrin at 150 mg/kg given to male mice in a single ip injection does not increase the ratio of early fetal deaths to the total number of implantations occurring in the uterus of the female mice to which they are mated.

A summary of the results of the animal studies, other than for carcinogenicity and mutagenicity, is presented in Table III-1.

Carcinogenicity

In 1963, Kotin and Falk [62] reported at a conference, and Falk confirmed in a written communication of September 1975, that skin papillomas and cancer of the lymphatic system and of the lungs were observed in C3H strain mice injected with epichlorohydrin. A dose of 5 μM in 0.1 ml of ethyl laurate or tricaprylin was administered in a single subcutaneous injection to each of 30 mice, which were then observed for about 2 years. Control animals were injected with either solvent. Four experimental animals developed malignant lymphomas at 3.25, 3.25, 5.5, and 6 months after the beginning of the experiment. The incidence of lymphomas in the control group was about half that observed in the experimental animals. In the mice injected with epichlorohydrin, there was a skin papilloma after 11.5 months, a hepatoma in another mouse after 13 months, and 2 lung adenomas in 1 mouse after 24 months. The control animals had occasional hepatomas and lung adenomas, but no skin papillomas. The survival of the epichlorohydrin-treated animals was poor. During the 1st year, 12 mice died; after the 2nd year, only a few survived. Falk noted that, except for the single skin papilloma, the tumors were generally of the same type and frequency of occurrence as in the control groups. Thus, the experiment was inconclusive.

In 1963, Weil et al [63] reported the results of a skin carcinogenic assay with 60 epoxy compounds, including epichlorohydrin, on 90-day-old C3H-strain mice. Hair was removed from the backs of about 40 mice and

undiluted liquid epichlorohydrin was painted onto the midline 3 times/week for 25 months. The amount of epichlorohydrin applied was not measured. At the end of 12 months, 37 mice survived; at the end of 17 months, 30 were alive; and, at the end of 24 months, only 1 survived. Examinations showed no tumors and no signs of toxicity. Based on the mortality rate, the authors stated that epichlorohydrin was the most toxic of the epoxides tested. The only control substance was methylcholanthrene, a positive control, which induced tumors. Thus, it can be concluded that, under the conditions of this experiment, dermally applied epichlorohydrin does not induce significant numbers of skin tumors in C3H-strain mice.

In 1974, Van Duuren et al [64] reported the final results of dermal application, subcutaneous injection, and ip injection of epichlorohydrin on female ICR/Ha Swiss mice. Previously, Van Duuren had published two papers reporting preliminary [65] and intermediate results. [66] Since the complete report is now available, [64] the earlier papers are not discussed in this document. In the skin-application experiments, 50 mice were shaved initially and whenever necessary during the experiment. A dose of 2.0 mg of epichlorohydrin in 0.1 ml of acetone was applied three times/week to the interscapular region. The test lasted for 580 days (83 weeks). Skin lesions were diagnosed as papillomas when they reached 1 cu mm in size and persisted for 30 days or more. No papillomas or carcinomas occurred in the animals to which epichlorohydrin, acetone, or nothing was applied.

A group of female ICR/Ha mice had 2.0 mg of epichlorohydrin in 0.1 ml of acetone applied to the skin followed 2 weeks later by three applications each week, and throughout the study (total duration, 385 days), of 2.5 μg

of phorbol myristate acetate (PMA), a promoter, in 0.1 ml of acetone. [65] In the group of 50 mice to which epichlorohydrin was applied, nine mice developed papillomas and one a carcinoma. Control animals to which solvent (30) alone or no chemical (100) was applied produced no tumors. Of the mice to which PMA alone (30) was applied, three developed papillomas.

For an assay by subcutaneous injection, 50 mice were injected weekly in the left flank with 1.0 mg of epichlorohydrin in 0.05 ml of tricaprylin. [64] This test also lasted for 580 days. Of the animals given epichlorohydrin, six developed sarcomas and one an adenocarcinoma (P value less than or equal to 0.05). In comparison, 1 mouse of 50 injected with tricaprylin alone developed sarcoma, and none of the control animals developed any tumors. The significance of subcutaneous sarcomas which occur at the injection site has been discussed by Grasso and Golberg. [49] In an ip assay, 30 mice received weekly injections into the lower abdomen of 1.0 mg of epichlorohydrin in 0.05 ml of tricaprylin. The experiment was terminated after 450 days. None of the mice developed local sarcomas, but 11 had papillary lung tumors. Of mice given tricaprylin alone, 10 had papillary tumors of the lungs and 1 developed a local sarcoma.

The results of these studies raise concern about an additional risk of carcinogenesis for the segment of human population continuously exposed to epichlorohydrin throughout the working lifetime. Available experimental evidence [67] indicates that the risk of induction of cancer in animals and in humans can be reduced by reducing the maximum allowed cumulative dose to which they are exposed. Based on these reports, further tests involving long-term inhalation exposures of animals to epichlorohydrin must be done to determine the degree of occupational risk following chronic inhalation

of epichlorohydrin. A tabular summary of results of the carcinogenic studies is presented in Table III-2.

Mutagenicity

Definitions of various terms used in this section are given in the Glossary, Appendix IV. [68,69]

One of the earliest mutagenicity studies was undertaken by Rapoport [70] who, in 1948, reported that epichlorohydrin induced 0.7% mutations (4 mutations in a total of 526 chromosomes) in Drosophila melanogaster. A control series showed no mutations (0 mutations in 887 chromosomes). Although lack of details about the experimental design prevents a thorough evaluation of this report, it provides evidence that epichlorohydrin induces mutations in this eukaryotic organism.

In 1951, Loveless [71] defined radiomimetic activity as a highly specific effect upon the resting cell producing an alteration in the genetic material. He postulated that this alteration can be shown by chromosome breakage and rearrangement in subsequent divisions. Root tip meristems of Vicia faba (broad bean) were treated with epichlorohydrin solutions of unspecified concentrations. Exposure was limited to 1 hour, and epichlorohydrin at a wide series of concentrations was tested. At 4-6 hours after treatment, samples were examined for immediate effects on those cells already in division at the time of treatment and again at 18, 24, 36, or 48 hours to determine the effect upon cells in the resting stage at the time of treatment. The author [71] rated epichlorohydrin as having a "low activity" but did not state what was meant by this term; he indicated that the results of this study would be discussed fully in a later paper.

However, such a report has not been found.

The induction of mutations in microorganisms has been used as an ancillary method to study genetic responses to environmental agents. [72] Microbiologic assays offer a number of unique experimental advantages over mammalian assays. They can use large populations so that they have the capacity to detect events which occur infrequently. Also, microbial test systems are available which can distinguish between mechanistically different classes of microscopic mutations (base-pair substitution and frameshift mutations) and macroscopic alterations (chromosomal translocations and deletions). All these genetic alterations have been observed in human populations. [7,72] However, routine mammalian mutagenicity test systems which are capable of detecting base-pair substitutions and frameshift mutations in the offspring of mammals are not simple or very practical. From a practical viewpoint, microbial assays are rapid and relatively inexpensive. With the exception of certain viruses, the genetic material of all organisms consists of deoxyribonucleic acid, often complexed with ribonucleic acid and protein. [72] It is, therefore, clear that evidence of mutation induced by a chemical in microbial systems is a cause for concern for human populations but does not provide a basis for establishing the degree of risk to human populations.

In 1955, Kolmark and Giles [73] studied the induction of mutations by epichlorohydrin and five other monoepoxides. A purple mutant of Neurospora crassa lacking adenine, strain 38701, was used for the induction of reverse mutation. The spontaneous mutation rate at the loci governing adenine independence for Neurospora crassa is 0.0008-0.029 mutations/100,000 gametes. [69] Epichlorohydrin at a concentration of 0.15

M was added directly to a suspension of macroconidia in sterile distilled water. The suspension was kept at 25 C and gently agitated for 15-60 minutes, centrifuged, and then washed. At various intervals, portions were then plated onto a minimal agar medium. Controls were treated similarly except that no epichlorohydrin was added to the suspension. The number of viable, surviving conidia was determined by plating diluted samples on minimal medium supplemented with adenine. Out of a million surviving conidia, 8.5 reverse mutations were induced when treated with epichlorohydrin for 15 minutes. When the treatment was for 60 minutes, 411 mutations/million surviving conidia were induced. Thus, under the optimal conditions of 0.15 M epichlorohydrin for a 45-minute exposure, 7.36 x 10*7 (* means "to the power of") conidia were treated and yielded 4,140 revertants. The background was 39 revertants; the survival was 41.5%. This yields an average value of 135.2 induced premutational lesions/million surviving conidia, or 20 premutational lesions/mole of epichlorohydrin/minute. The biochemical nature of the original mutations in the conidia that were reversed by epichlorohydrin was not discussed. This test gives an underestimate of the true back-mutation frequency at this locus, since macroconidia were tested, and, if each such conidium contained three nuclei, a reversion in more than one nucleus would still be scored as a single revertant.

In 1960, Strauss and Okubo [74] reported the mutagenic actions of ultraviolet radiation and alkylating agents. One of the alkylating agents selected was epichlorohydrin. A tryptophan-requiring mutant of Escherichia coli, strain B/r, was used. The measure of mutation was the change from tryptophan requirement to independence, a reverse mutation. The number of

revertants present in a particular sample was determined by plating a 0.1-ml portion of the bacterial suspension on plates of minimal medium on a tryptophan-free nutrient agar. The total number of viable cells was determined by plating after dilution on nutrient agar containing tryptophan. The cells from overnight cultures were collected, washed twice with 0.1 M phosphate buffer of pH 7.2, and suspended in the same buffer at approximately 7 x 10*8 cells/ml. Epichlorohydrin (2 ml) was suspended in 3 ml of ethanol, but it did not go completely into solution. One milliliter of this mixture was added to 100 ml of the bacterial suspension and 1-ml portions were removed and plated without being washed. Cells were plated on either minimal agar or minimal agar supplemented with a small amount of nutrient broth to allow several divisions of the cells to enhance the expression of the revertant phenotype. Cells were also harvested, washed to remove excess epichlorohydrin, and resuspended in the buffer before plating. In the control, there were 2.2 x 10*8 viable cells plated. A total of 6.4 revertants/10*8 cells plated on the minimal medium and 11.4 revertants/10*8 cells plated on the minimal medium containing the nutrient broth were observed. When cells were harvested immediately after the addition of epichlorohydrin, there were 1.7 x 10*8 viable cells plated. Cells plated on the minimal medium showed 0.3 revertants/10*8 cells. Cells plated on the medium containing the broth showed 28.0/10*8 revertants. When cells were incubated with epichlorohydrin for 15 minutes before harvesting, there were 1.5 x 10*8 viable cells plated. There were no revertants in the cells plated on the medium alone and 38.3/10*8 revertants in cells plated on the medium containing the broth. Thus, the revertants are calculated to have increased at the rate of 30 premutational

lesions/mole of epichlorohydrin/minute during the 60-minute treatment. Survival was approximately 80% at the end of the treatment.

In 1973, Mukai and Hawryluk [75] reported testing epichlorohydrin in Escherichia coli and in Salmonella typhimurium. Since the details of the tests were not given, Mukai (written communication, October 1975) reported that 11.8 mg of epichlorohydrin in 0.1 ml of dimethyl sulfoxide was applied to sterile filter paper disks and placed in the center of duplicate test plates. Base-pair substitutions in Escherichia coli and both base-pair substitutions and frameshift mutations in Salmonella typhimurium were induced by epichlorohydrin. He further reported that greater than twentyfold increases in revertants over control plates were observed in both organisms.

In 1973, Voogd [76] reported in an abstract testing several epoxy compounds, including epichlorohydrin, for their abilities to induce mutations in a Klebsiella pneumoniae auxotroph requiring uracil and proline for growth. Mutations to streptomycin resistance were scored. The author stated that nearly all the tested substances displayed a certain degree of mutagenicity and that the mutagenic activity of the epoxy group was often slightly increased by electrophilic groups on carbon atoms next to the epoxy group. Voogd provided additional information in a written communication of October 1975. Increases in mutations in both Klebsiella pneumoniae and Salmonella typhimurium were induced by epichlorohydrin. The experiment was a Luria-Delbruck fluctuation test, [77] so that a true mutation rate, and not a mutation frequency, was measured. In the Klebsiella pneumoniae assay, the mutation frequency was based on a forward mutation to streptomycin-resistance or streptomycin-dependence. In

general, such mutations alter a ribosomal protein, and chemicals which cause frameshift mutations or lead to deletions are not detected as mutagens in such an assay. The cells were suspended in broth in a concentration of 100 cells/ml, and 105 samples of 2.5 ml were treated for 20 hours with 0.00637 M epichlorohydrin. After treatment with epichlorohydrin, the maximum reported frequency of mutations was 7.617/10*9 or 45.4 times the background of 0.1676/10*9. In the Salmonella assay, his G-46, TA1530, TA1535, TA100, and TA98 strains were also tested for mutagenesis by a procedure similar to the Klebsiella assay. The first four strains contain the same base-pair substitution mutation. The reverse mutation to histidine-independence was increased in all four strains by 0.001 M epichlorohydrin. Strain TA98 contains a frameshift mutation and did not revert when treated with epichlorohydrin.

Recently, workers exposed to epichlorohydrin were monitored for the presence of mutagens in their urine (DJ Kilian, written communication, April 1976). The study group included six people exposed to epichlorohydrin at concentrations from 0.8 to 4.0 ppm, measured as 8-hour TWA concentrations, and two people exposed by a large epichlorohydrin spill that generated a concentration in air in excess of 25 ppm. Five subjects who had not been exposed to epichlorohydrin served as controls. Mutagenic activity was evaluated using Salmonella typhimurium strains 1535, 1537, 1538, 100, and 98. Results are summarized in Table XIII-3. All samples except the two from individuals with high exposures were comparable with those from the control subjects; preparations derived from the urine of these two individuals indicated the presence of materials which influenced the genetic mechanism of Salmonella typhimurium. With the 1535 strain, an

increase in mutants in excess of twofold over the control was evident. In strain 1537, a statistically significant decrease in the number of mutants, relative to the controls, was observed. Although there were only six people in the data base, this report does indicate that exposure to high concentrations of epichlorohydrin may give positive results. While it is not possible to draw any dose-effect relationship from this small group of subjects, the results of the study tend to indicate that a genetically active material is present within the human body after a sufficiently large exposure to epichlorohydrin.

In summary, the induction of reverse mutations by epichlorohydrin in N crassa, [73] E coli, [74] and S typhimurium, [75] and forward mutations in K pneumoniae [76] have been observed. Most of the microbial mutations could be accounted for by base-pair substitutions. Following exposure to epichlorohydrin, mutations have occurred in the fruit fly (Drosophila melanogaster). [70] Thus, apparently epichlorohydrin can induce point mutations in some organisms, both prokaryotic and eukaryotic. Other than the dominant lethal assay, [61] reports of experiments designed to detect epichlorohydrin-induced inheritable genetic alterations in mammals have not been found, so that a reasonable basis for estimating the risk to the human population has not been established. However, it has been shown that a substance that can induce mutations is present in the urine of people who are overexposed to epichlorohydrin (DJ Kilian, written communication, April 1976). The results of the mutagenicity experiments discussed in this section are summarized in Table III-3.

Correlation of Exposure and Effect

Occupational exposure to epichlorohydrin occurs chiefly by inhalation and skin contact and, to a limited extent, by ingestion. Cases of delayed skin burns resulting from contact with epichlorohydrin in the occupational environment have been reported. [35] Burning, itching, blisters, skin erosion, redness, and residual erythema have been the usual signs. Usually, there has been a latent period of a few minutes to several hours between the dermal contact and the resulting effects. The severity of the burns has been dependent upon the duration of the contact. One worker who failed to remove his epichlorohydrin-contaminated shoes for 6 hours developed severe skin damage with painful, enlarged lymph nodes in the groin; he was hospitalized for 22 days. Another worker who washed his hands with soap and water after wiping up an epichlorohydrin-methanol mixture from the floor developed itching, burning, redness, and swelling, and was hospitalized for 11 days. Edema, ulceration, hyperemia, and necrosis of rabbit skin resulting from dermal application of epichlorohydrin also have been observed. [27,29] Kremneva and Tolgskaya [27] reported also that, when the tails of 10 mice were immersed for an hour in test tubes containing epichlorohydrin, 6 animals died within 3 days.

Thus, experience in both humans [35] and animals [27,29] indicates that epichlorohydrin may induce, in addition to severe damage to the skin, systemic poisoning following dermal absorption. The intensity of these effects appears to increase with the dose and the duration of exposure.

There are very few reports of the effects on humans of epichlorohydrin inhalation. [11,33,37,38] One report [33] involved a

worker who was acutely exposed to epichlorohydrin at an unspecified but probably very high concentration. Eye and throat irritation, nausea, vomiting, headache, and dyspnea were the immediate effects. Bronchitis, liver damage, and hypertension were detected during the 2 years following the accident. An industrial report [37] stated that exposure to epichlorohydrin at 100 ppm, even for a short period, would be intolerable to humans. This was based on the observation that exposure to epichlorohydrin at 40 ppm for an hour caused eye and throat irritation lasting 48 hours and that exposure at 20 ppm for one hour caused temporary burning of the eye and nasal passages. Wexler [38] reported that exposure to epichlorohydrin at concentrations greater than 100 ppm induced lung edema and kidney lesions in humans. Pet'ko et al [11] observed changes in the reticulocyte count, bilirubin, cholesterol, and protein concentration of the blood in people occupationally exposed to epichlorohydrin. These changes were not statistically significant. An epidemiologic study (DJ Kilian, written communication, April 1976) of workers exposed to epichlorohydrin revealed no abnormalities. Because of the lack of a control group, lack of information on the exposure concentrations, and because the longest exposure period was only 16 years, it is difficult to make any final conclusions regarding chronic effects, especially those with long latent periods.

Fomin [28] reported that inhalation of epichlorohydrin at 0.08 ppm induced statistically significant (P value not given) changes in the EEG recordings in all of five volunteers; no effects were observed at a concentration of 0.05 ppm. Since the exposure period was not given, it is not possible to estimate the dose of epichlorohydrin absorbed. If the

concentrations stated in this paper are correct, it can be concluded from this study that inhalation of epichlorohydrin at 0.08 ppm induces measurable effects on brain function in humans.

Epichlorohydrin-induced sterility in animals has been reported. [39,41] Cooper et al [39] found that 12 repeated doses of epichlorohydrin at 100 mg/kg caused an apparently permanent sterility of male rats as indicated during a 12-week period, while Hahn [41] found that the dose of 15 mg/kg/day of epichlorohydrin produced a reversible sterility. It can be concluded that, in rats, epichlorohydrin causes sterility which is both dose and time dependent. The induction of sterility following repeated doses of 15 mg/kg is another example of the time-dependent cumulative nature of effects induced by epichlorohydrin. The results from the experiments in mice and rats are insufficient to permit any inference of the rate at which epichlorohydrin must be absorbed to induce inheritable genetic alterations in the offspring of mammals, although the evidence suggests that epichlorohydrin may influence the spontaneous mutation rate in mammals.

Animal studies in which inhalation was the principal route of entry have been extensively reported. [26-28] Gage [26] found that labored breathing, profuse nasal discharge, loss of weight, leukocytosis, increased urinary protein concentration, and peripheral atrophy of the cortical tubules in the kidney occurred in rats exposed to epichlorohydrin at 120 ppm. Respiratory distress, nasal discharge, and weight loss were evident in rats inhaling epichlorohydrin at 56 ppm; these effects were still present but less severe at 27 ppm. No effects were observed on rats exposed to epichlorohydrin at 17 ppm; however, at 9 ppm, pulmonary

infection occurred in two rats. Fomin [28] reported increases in leukocytes with altered fluorescence and urinary coproporphyrin, accompanied by decreases in the nucleic acid content of the blood, in rats exposed to epichlorohydrin at 5 ppm; in addition, lung and kidney damage were present. Some of these effects were also present in rats exposed to epichlorohdyrin at 0.5 ppm, while none were observed at 0.05 ppm. Kidney damage and disrupted liver function were observed in animals exposed at 5.2 and 1.8 ppm. [32] From these studies, it can be concluded that epichlorohydrin causes liver and kidney damage in animals. There are two conditions of exposure at which epichlorohydrin induced no effects: 27 ppm, 6 hours/day, for 18 days [26] and 0.05 ppm, 24 hours/day, for 98 days. [28]

Carcinogenicity, Mutagenicity, and Teratogenicity

Van Duuren et al [64] have reported that epichlorohydrin induces tumors in mice at subcutaneous injection sites when administered alone. Weil et al [63] and Van Duuren et al [64] found that epichlorohydrin induced no tumors in mice by skin painting assay. The data of the skin applications followed by a promotor suggest that epichlorohydrin may initiate the carcinogenic process in mice. [64] Weekly ip injections of 1.0 mg epichlorohydrin resulted in 11 of 30 mice developing papillary lung tumors, which was similar to the observations in the control group.

The induction of mutations following exposure to epichlorohydrin in microbial species has been reported. [71,73,75] The experiments indicate that epichlorohydrin can induce base-pair substitution mutations. It is evident that epichlorohydrin induces a high frequency of mutations in

fungi, [71] microbial organisms, [73-76] and in the fruit fly. [70] The most plausible molecular basis of the epichlorohydrin-induced mutations in all of these organisms is the covalent bonding of epichlorohydrin to the cellular genetic material, DNA. In view of the virtual irreversibility of these reactions, the degree of genetic damage may be expected to increase with exposure time in these lower organisms as well as in higher forms. [78]

Reports of experimental attempts to induce the formation of terata by exposing pregnant female animals to epichlorohydrin have not been found.

TABLE III-1

EFFECTS OF EPICHLOROHYDRIN IN ANIMALS

Routes of Exposure	Animals	No.	Exposure Concentration and Duration	Effects	Reference
Inhalation	Mice	30	16,600 ppm 30 min	Nose and eye irritation, mortality 100%	25
"	"	20	8,300 ppm 30 min	Mortality 100%	25
"	"	10	2,370 ppm 1 hr/d x 16 d	"	25
"	"	30	2,370 ppm 1 hr	No deaths	25
"	Rats	6	250 ppm 4 hr	Death of 2-4 rats	58
"	"	8	120 ppm 6 hr/d 5 d/wk x 11 d	Labored breathing, profuse nasal discharge, weight loss, leukocytosis, increased urinary protein, peripheral atrophy of cortical tubules	26
"	"	60	91.0 ppm 4 hr	Kidney damage, liver function disrupted	32
"	"	60	5.2 ppm 4 hr	"	32
"	"	60	1.8 ppm 4 hr	Kidney damage and disrupted liver function less severe than with 91.0 and 5.2 ppm	32
"	"	8	56 ppm 6 hr/d 5 d/wk x 18 d	Respiratory distress, nasal discharge, weight loss	26

TABLE III-1 (CONTINUED)

EFFECTS OF EPICHLOROHYDRIN IN ANIMALS

Routes of Exposure	Animals	No.	Exposure Concentration and Duration	Effects	Reference
Inhalation	Rats	8	27 ppm 6 hr/d 5 d/wk x 18 d	Mild nasal irritation	26
"	"	8	17 ppm 6 hr/d 5 d/wk x 19 d	No effects	26
"	"	8	9 ppm 6 hr/d 5 d/wk x 18 d	Pulmonary infection	26
"	"	15	5.2 ppm 24 hr/d x 98 d	More leukocytes with altered fluorescence, increased urine coproporphyrin, kidney and lung damage, decrease in blood nucleic acid	28
"	"	15	0.5 ppm 24 hr/d x 98 d	Increased modified leukocytes, reduced blood nucleic acid	28
"	"	15	0.05 ppm 24 hr/d x 98 d	No effect	28
Subcutaneous	"	120	500 mg/kg 250 mg/kg 125 mg/kg	Reduced blood histamine activity	42
"	"	14	180 mg/kg	Necrotic lesions in nephrons; nonspecific lung, brain, and adrenal gland damage	30
"	"	23	150 mg/kg	"	30

TABLE III-1 (CONTINUED)

EFFECTS OF EPICHLOROHYDRIN IN ANIMALS

Routes of Exposure	Animals	No.	Exposure Concentration and Duration	Effects	Reference
Subcutaneous	Rats	-	150 mg/kg	LD50	29
"	"	67	125 mg/kg	Oliguria, anuria, polyuria, kidney damage	46
"	Mice	10	0.23 ml/kg/d x 4 d	Mortality 100%	25
"	"	10	0.08 ml/kg/d x 21 d	"	25
Oral	"	15	0.5 ml/kg	"	25
"	"	15	0.23 ml/kg/d x 4 d	"	25
"	"	15	0.23 ml/kg	No deaths	25
"	"	-	0.20 ml/kg	LD50	31
"	"	15	0.08 ml/kg/d x 21 d	Mortality 100%	25
"	Rats	-	0.22 ml/kg	LD50	31
Dermal	Rabbits	-	0.64 ml/kg	LD50	31
"	Rats	20	2 ml/kg x 1 hr	Mortality 80%, local irritation	25
"	"	10	1 ml/kg x 1 hr x 3	Mortality 40%, local irritation	25
"	"	10	1 ml/kg x 1 hr	Mortality 20%, local irritation	25

TABLE III-1 (CONTINUED)

EFFECTS OF EPICHLOROHYDRIN IN ANIMALS

Routes of Exposure	Animals	No.	Exposure Concentration and Duration	Effects	Reference
Dermal	Rats	10	0.5 ml/kg x 1 hr x 4	Mortality 100%, local irritation	25
"	"	10	0.5 ml/kg x 1 hr	Local irritation, no deaths	25
iv	Cats	-	0.08 ml/kg	Minimum lethal dose	25
"	"	3	0.008 ml/kg	Transitory fall in blood pressure	25
"	Dogs	-	0.08 ml/kg	Minimum lethal dose	25
"	"	2	0.008 ml/kg	Transitory fall in blood pressure	25
ip	Mice, rats, guinea pigs, and rabbits	-	0.10 to 0.14 ml/kg	LD50	31

TABLE III-2

CARCINOGENIC EFFECTS OF EPICHLOROHYDRIN IN MICE

Routes of Exposure	Strain	No.	Exposure Concentration and Duration	Effects	Reference
Subcutaneous	C3H	30	5 μM	4 malignant lymphomas, (about double the control value)	Falk*
"	ICR/Ha Swiss	50 F	1 mg** 1/wk x 83 wk	1 adenocarcinoma, 6 sarcomas	64
Controls	"	50 F	vehicle only	1 sarcoma	
ip	"	30 F	1 mg** 1/wk x 64 wk	11 papillary lung tumors	64
Controls	"	30	vehicle only	10 papillomas 1 sarcoma	
Painting on clipped backs	C3H	27 - 30	Undiluted 3/wk x 25 mon	0 tumors	63
Application to shaved backs	ICR/Ha Swiss	50 F	2.0 mg in 0.1 ml acetone 3/wk x 83 wk	"	64
"	"	30 F	2.0 mg in 0.1 ml acetone***	9 papillomas, 1 carcinoma	64
"	"	30 F	controls****	3 papillomas	

*(H Falk, written communication, September 1975)
**Dissolved in 0.05 ml tricaprylin
***Beginning 2 weeks after the one epichlorohydrin application, 2.5 μg of PMA was applied three times/week for 53 weeks.
****2.5 μg of PMA only was applied three times/week for 53 weeks.

TABLE III-3

MUTAGENICITY STUDIES

Species	Dose	Results	Reference
Drosophila melanogaster	Unspecified	Epichlorohydrin-induced mutations, 0.7%; none in control series	70
Neurospora crassa	0.15 M	Epichlorohydrin-induced premutational lesions, 20/mole/minute, over the background	73
Escherichia coli	0.017 M	Epichlorohydrin-induced (reverse) premutational lesions, 30/mole/minute, over the background	74
Escherichia coli	1.27 M in dimethyl-sulfoxide	A 20-fold increase in revertants over control	75
Salmonella typhimurium	"	"	75
Klebsiella pneumoniae	0.00637 M	A 45.4-fold increase in mutations over background	76
Salmonella typhimurium	0.001 M	An increased number of induced mutations over control	76

IV. ENVIRONMENTAL DATA AND ENGINEERING CONTROLS

Environmental Data

Dow Chemical Company [2] reported personnel monitoring data by job classification for its units which produce allyl chloride, epoxy resin, and glycerine. Sampling was conducted with charcoal tubes using a calibrated, battery-operated pump. Quintuplicate samples were taken for each job classification at a rate of 2 liters/minute for 7 hours. Epichlorohydrin and chlorinated hydrocarbons were extracted with 30 ml of carbon disulfide. Epichlorohydrin recovery from the charcoal, after sampling, was found to be 65%. Analysis was performed with a hydrogen flame chromatograph equipped with a 12 feet x 1/8 inch column packed with 15% Oronite NiW on gas chrom CLA (60-80 mesh). In 1973, in the epoxy resin unit, one air sample in the breathing zone of each of four employees (three operators and one helper) showed the average epichlorohydrin concentration to be 0.03 ppm. In the same year, 78 grab samples indicated that epichlorohydrin concentrations ranged from 13 ppm to less than 0.60 ppm, with an average of 3.17 ppm. It should be noted that the "average" was a numerical average between the individual samples, not the TWA concentrations. The results of air monitoring done in 1974 are presented in Table IV-1. In the glycerine distribution unit, five air samples in the breathing zones of an operator, two for the head operator, and two for the technician showed epichlorohydrin concentration to be below 0.01 ppm. These were taken in 1975. Results of air monitoring for epichlorohydrin done in the glycerine plant in 1975 are presented in Table IV-2. Epichlorohydrin concentrations in the allyl chloride unit were below 0.1 ppm.

TABLE IV-1

EPICHLOROHYDRIN CONCENTRATIONS IN THE AIR IN AN EPOXY-PRODUCING UNIT (1974)

Job Classification	No. Samples	Epichlorohydrin (ppm v/v)		
		High	Low	Average
Warehouse operator	4	0.30	0.30	0.30
Machinist	1	0.10	0.10	0.10
Pipefitter	2	0.30	0.30	0.30
Control C operator	3	0.90	0.40	0.66
2d class operator BIS	1	0.10	0.10	0.10
Grab samples	25	15.00	0.60	2.02
Stationary monitoring	23	1.00	0.10	0.26

From reference 2

TABLE IV-2

EPICHLOROHYDRIN CONCENTRATIONS IN THE AIR IN A GLYCERINE-PRODUCING UNIT (1975)

Job Classification	No. Samples	Epichlorohydrin (ppm v/v)		
		High	Low	Average
Control "A"	5	1.37	0.24	0.54
Instrument	2	0.01	0.01	0.01
Lab	6	0.67	0.01	0.11
Shift foreman	3	0.24	0.01	0.08
EPI helper	4	0.18	0.01	0.05
Control "A" finishing	2	0.01	0.01	0.01
Maintenance	13	4.69	0.01	1.50

From reference 2

Pet'ko et al [11] reported the results of environmental monitoring done in epichlorohydrin and dichlorhydrin-glycerine production units in Russia. The sampling technique employed was not specified. Concentrations of epichlorohydrin ranged from 19 to 21 mg/cu m (4.9-5.5 ppm) in the zone of employees who withdrew samples for quality control from the epichlorohydrin-production process. Airborne concentration of epichlorohydrin reached 12-15 mg/cu m (3.1-3.9 ppm) during the filling of tanks with epichlorohydrin. During an emergency caused by mechanical difficulties, a concentration range of 210-211 mg/cu m (54.6-54.9 ppm) was recorded.

Fomin [28] reported that, at about 100-200 meters from a factory discharging epichlorohydrin into the atmosphere, the airborne epichlorohydrin concentration exceeded the maximum permissible concentration of 0.2 mg/cu m by factors of 2.5-6. At a distance of 400 meters, 5 of 29 samples indicated that epichlorohydrin concentrations exceeded the 0.2 mg/cu m limit. No epichlorohydrin was detected at distances of 500-600 meters from the factory.

Sampling and Analysis

There are many general methods of sampling and analysis for organic vapors. A few of these have been adapted or found suitable for epichlorohydrin.

Impingers or bubblers containing distilled water have been used for epichlorohydrin vapor collection. [38,79] A 2-liter air sample is drawn

through two bubblers in series, containing 8 ml of water each, at a sampling rate of 0.5 liter/minute. [79] When a test atmosphere was used, the percentage of epichlorohydrin trapped in the first bubbler decreased as the atmospheric concentration decreased. At a concentration of 20 mg/cu m (approximately 5.2 ppm), the efficiency of one bubbler was 80%. For greater accuracy, two bubblers were recommended. The main disadvantage of such a sampling system is the difficulty in obtaining a personal sample. Since the collection medium is liquid, some sample loss can occur from spillage and evaporation. Epichlorohydrin vapor has also been collected in bubblers containing sulfuric acid. [80]

Plastic bags [81-84] and glass bottles [85] have been used for sampling industrial air. Usually, this has involved obtaining a volume of air over a very short time, from a few seconds to 2 minutes. Such sampling techniques are best suited for obtaining information on ceiling concentrations. However, sampling with plastic bags has been modified to determine TWA concentrations. [84] Aluminum foil-polyester laminate bags or Teflon bags were used. The advantage of this technique is that both TWA and excursion values can be estimated. However, 24-hour sample losses were 20-26% and 19-40% for epichlorohydrin stored in Teflon and aluminum foil-polyester laminate bags, respectively. These losses occurred when the epichlorohydrin concentration in the air sampled ranged from 5 to 27 ppm. [84] Bulkiness of the containers has created transportation problems.

Adsorption on silica gel [80,86,87] or activated charcoal [88-90] is commonly used to collect organic vapors. Reid and Halpin [91] found charcoal tubes both efficient and practical for sampling a number of chlorinated hydrocarbons. At present, a major manufacturing company uses

charcoal tubes for sampling epichlorohydrin. [2] Epichlorohydrin in air has been sampled at 20-30 liters/hour through a glass tube (45-mm long and 3 mm in diameter) containing 0.1 g silica gel. [80] Data on collection efficiency were not given. However, sampling with silica gel in high humidity may result in considerable sample loss from the displacement of the organic vapors by water vapor. Whitman and Johnston [92] reported that this problem could be overcome with a molecular sieve prefilter. They used a 5-Angstrom molecular sieve to remove water vapor from gas streams without interfering with the passage of aromatic hydrocarbons. White et al [89] have described the design of activated charcoal tubes suitable for sampling, and such tubes are commercially available. Adsorption on activated charcoal is the preferred sampling method for epichlorohydrin alone for several reasons: epichlorohydrin is not displaced by water vapor as it is from silica gel; it is a simpler, more convenient procedure than the use of plastic bags or of a bubbler; it uses a small, portable sampling device, and the difficulties associated with handling liquids are eliminated. Disadvantages are that the amount of sample that can be collected is limited by the number of milligrams that the charcoal tube will hold before overloading, and that the more volatile compounds can migrate to the backup section during storage before analysis.

Various methods used for analyzing the collected samples have included colorimetry, [79,80] infrared analysis, [93,94] and gas chromatography. [90,95] Colorimetric analysis suitable for analyzing epichlorohydrin in an aqueous solution has been used. [79] The colorimetric method [79] is based on the oxidation of epichlorohydrin in aqueous solution by periodic acid. Epichlorohydrin in water is hydrolyzed

to a glycol which is then oxidized to formaldehyde. Epichlorohydrin solutions of known concentrations are prepared to obtain the standard curve. The formaldehyde further reacts with sodium arsenite and acetylacetone reagent to form a yellow complex. The acetylacetone reagent solution is prepared by mixing ammonium acetate, acetylacetone, and glacial acetic acid in water. Maximum optical density of the yellow complex occurs at about 412 nm. This method was capable of determining as little as 20μg of epichlorohydrin. Data on the efficiency of the analytical technique were not given. [79] Formaldehyde, or any substance that may yield formaldehyde under the test conditions, will interfere. Compounds that contain or would form vicinal terminal hydroxy groups, such as ethylene glycol and ethylene oxide, will also interfere.

A colorimetric method [80] suitable for analyzing epichlorohydrin collected in sulfuric acid also has been used. Air containing epichlorohydrin was drawn through two bubblers containing 3 ml of 20% sulfuric acid and 4 ml of 10% sulfuric acid, respectively. The content of the first bubbler was diluted 1:1 with water. A 3-ml sample was then oxidized with 0.5 ml of 3% potassium iodate solution and allowed to stand for 30 minutes, during which time a yellow color developed. A 10% sodium sulfite solution was added and the mixture was shaken until the color disappeared. One milliliter of Schiff's reagent was then added and the intensity of the resulting color (magenta) was measured 1 hour later. The initial reactions occurring were similar to those in the previously discussed colorimetric method. [79] Epichlorohydrin is hydrolyzed by sulfuric acid and the resulting glycol is oxidized to formaldehyde by the iodate. The formaldehyde then reacts with Schiff's reagent to form a

magenta complex. Sodium sulfite is added to reduce the unreacted iodate. It was found that this method was capable of analyzing 0.01-0.1 mg epichlorohydrin in a 6-ml solution. Data on sensitivity, specificity, and interferences were not reported. However, the same compounds that would interfere with the previously discussed colorimetric technique, [79] such as ethylene oxide and ethylene glycol, would also interfere with this method. In addition, many aldehydes would interfere.

The formaldehyde can also react with phenylhydrazine hydrochloride to form phenylhydrazone. [38] The phenylhydrazone of formaldehyde reacts with potassium ferricyanide to form a colored complex. The maximum optical density of this complex occurs at about 500 nm. Epichlorohydrin concentrations ranging from 0.45 to 14 mg/cu m in air were determined by this method. Precision tests indicated the maximum error between the two determinations to be only 0.3%.

The infrared absorption spectrum of epichlorohydrin showed the typical terminal epoxide absorption bands. [93] The minimum amount of epichlorohydrin that was detected by infrared absorption was 0.3% (v/v in aqueous solution). [94] However, a practical and detailed technique using infrared analysis for a quantitative determination of epichlorohydrin has not been developed.

In recent years, gas chromatography has become the method of choice of most investigators for separation and the analysis of organic materials. [89,90] It offers excellent specificity and sensitivity and is suitable for analyzing samples of airborne contaminants collected on charcoal. Interferences are few, and most of those which do occur can be eliminated by altering the instrumental conditions. Muganlinsky et al [95] developed

a linear temperature program to analyze epichlorohydrin in the presence of chlorinated hydrocarbons which may be present as impurities.

The recommended methods for sampling and analyzing epichlorohydrin are collection by charcoal tube and analysis by gas chromatography. Sampling involves the collection of personal samples on charcoal tubes, and analysis involves desorption with carbon disulfide and measurement with a gas chromatograph equipped with a suitable detector. [90] Details of the recommended methods are given in Appendices I and II. The recommended methods are not validated for monitoring or for an environment that may contain other substances that may interfere. Other sampling and analytical methods equivalent in accuracy, precision, and sensitivity may be used.

Engineering Controls

Engineering design for safety in working with epichlorohydrin should be such as to reduce the concentration of airborne epichlorohydrin. Closed systems, properly operated and maintained, should be used in all cases where practicable. Frequent tests must be conducted for leaks in closed systems. Where closed systems are not feasible, well-designed local exhaust ventilation systems must be provided. Guidance for design can be found in Industrial Ventilation--A Manual of Recommended Practice, [96] or more recent revisions, and in Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1971. [97] In operations where epichlorohydrin is transferred, changed, or discharged into otherwise normally closed systems, continuous local exhaust should be provided at the transfer point. Sufficient ventilation with clean air should be maintained

in the area to permit the correct operation of the local exhaust system.

Respiratory protective equipment is not an acceptable substitute for proper engineering controls but should be available in emergencies and for nonroutine maintenance and repair work situations.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

In 1965, the American Conference of Governmental Industrial Hygienists (ACGIH) adopted a threshold limit value (TLV) of 5 ppm (approximately 19 mg/cu m) for epichlorohydrin. [98]

In a personal communication cited in the Documentation of Threshold Limit Values for Substances in Workroom Air, [99] Smyth and Pozzani stated that cases of skin burns and sensitization, with resulting intolerance to trivial exposures, occurred in workers during the handling and production of epichlorohydrin. Systemic poisoning caused by epichlorohydrin penetration of the skin also was reported. Therefore, the ACGIH epichlorohydrin TLV listing was accompanied by a "skin" notation. [99] Such a notation refers to the potential contribution to overall exposure by the cutaneous route, including mucous membranes and eyes, either by airborne or, more particularly, by direct skin contact with liquid epichlorohydrin. This designation is intended to indicate the need for appropriate measures for the prevention of cutaneous absorption so that the TLV is not invalidated.

The present federal standard (29 CFR 1910.1000) for occupational exposure to epichlorohydrin is 5 ppm as an 8-hour TWA limit. This standard was based on the ACGIH TLV.

In Russia and in France, the maximum allowable concentration (MAC) in the industrial environment is 1 mg/cu m (0.26 ppm). [100] In the Rumanian Socialist Republic, 10 mg/cu m (approximately 2.6 ppm) of epichlorohydrin is the maximum concentration allowed in the occupational environment. [38]

In the Federal Republic of Germany, the permissible environmental exposure limit is 18 mg/cu m (approximately 3.6 ppm), and 5 mg/cu m (approximately 1 ppm) in the German Democratic Republic. [100] The bases for these standards are not given. Air and water quality standards have not been found, although one recommendation of such a value (0.2 mg/cu m) has been presented. [28]

Basis for the Recommended Standard

The induction of severe necrotic lesions occurring after dermal contact with epichlorohydrin has been reported. [35] A latency period lasting from several minutes to several hours between contact with liquid epichlorohydrin and the appearance of skin damage was observed. Epichlorohydrin penetrates the skin and can induce adverse systemic effects following dermal contact. [25,27,35] These necrotic lesions have been compared with those induced by X-rays or by other alkylating agents such as ethylene oxide or propanesultone. [35] These observations require, therefore, that complete skin protection be provided to employees handling epichlorohydrin. Care must be taken to ensure that shoes, gloves, and other protective clothing are made of material impervious to epichlorohydrin.

Reports on humans occupationally exposed to epichlorohydrin have identified the effects resulting from acute exposure. [28,37,38] Transient burning of the eyes and nasal passages in persons after exposure to epichlorohydrin at a concentration of 20 ppm was reported, [37,38] while exposure at 40 ppm caused eye and nasal irritation lasting 48 hours. [37,38] Lung edema and kidney lesions were reported in humans exposed to

epichlorohydrin at concentrations greater than 100 ppm for very short periods. [37,38] Changes in the voltage of the peaks of the alpha rhythm of the EEG measurements of volunteers exposed to epichlorohydrin at 0.08 ppm for a few minutes were reported by Fomin. [28] Since the significance of the changes observed in this component of the EEG measurements is not known, further research needs to be conducted in this area before any interpretations can be made. Acute exposure to epichlorohydrin at a high, but unknown, concentration [33] caused irritation of the eyes and throat, nausea, and dyspnea; bronchitis with bronchiolar constrictions and enlarged liver were suspected to have resulted from this single overexposure. These findings [28,37,38] suggest that a ceiling is required. Since acute effects have been observed on humans at 20 ppm, and the lowest concentration which induces effects during a short interval has not been identified, a ceiling concentration of 19 mg/cu m (5 ppm), based on professional judgment, is recommended to protect even the more sensitive fraction of the working population from these adverse effects.

The existing federal standard of 5 ppm is based on the 1968 TLV. Further information on cumulative aspects of toxicity such as sterility, carcinogenesis, and mutagenesis have been reported in subsequent studies. [28,31,32,39,64-66,74]

The report by Shumskaya et al [32] indicated that disrupted liver function and kidney damage developed in rats after single 4-hour exposures to epichlorohydrin at concentrations of 91, 5.2, or 1.8 ppm, the effects being least severe at 1.8 ppm. The authors did not indicate whether the chamber was static or dynamic. Thus, data from this study suggest that minor adverse effects are observed on animals inhaling a total amount of

1.0 mg/kg within 4 hours. The data demonstrate the induction of measurable biochemical perturbations, but cannot be used to predict the cumulative effects to be expected from long-term exposures to epichlorohydrin.

Kremneva and Tolgskaya [27] have reported neither mortality nor signs of intoxication in rats exposed for 3 hours at about 5.2-15.6 ppm daily for up to 6.5 months. Lags in body weight gains, initial increases in the excitability thresholds, elevations in blood pressures, and fluctuations in oxygen consumptions were observed in the animals when compared with the controls. They concluded that 5.2-15.6 ppm of epichlorohydrin approximated the threshold in rats, which is interpreted to mean that no measurable adverse effects occurred below these concentrations.

The minimal concentration which has been observed to induce effects on rats (about 5 ppm) is used to approximate the permissible exposure in the occupational environment by weighing additional risk factors. The chronic effects for which risk must be considered are carcinogenesis, mutagenesis, and antifertility, as well as liver, kidney, and lung damage.

Van Duuren et al [64] found that a single application of 2.0 mg of epichlorohydrin on mouse skin initiated the tumorigenic process in at least 9 of the 30 experimental mice when it was followed by triweekly applications of a promoter (phorbol myristate acetate) for the remainder of the 385-day experiment. The promoter alone induced papillomas in 3 of 30 mice. No initiation was observed in the control animals. Weil et al [63] and Van Duuren et al [64] found that repeated applications of epichlorohydrin on mouse skin did not induce a significant number of skin lesions. Van Duuren et al [64] found that sarcoma and adenocarcinoma were induced in 6 of 50 mice given weekly subcutaneous injections of 1.0 mg of

epichlorohydrin in 0.05 ml of tricaprylin (P values less than 0.05). Only 1 of the 50 control animals injected with tricaprylin alone developed sarcoma. No sarcomas developed in untreated control animals. The results were considered significant only when the P value was less than or equal to 0.05.

Antifertility effects, including persistent sterility, have been induced in animals exposed to epichlorohydrin. [39-41] Twelve repeated oral doses of 15 mg/kg of epichlorohydrin sterilized male rats. [41] Even though sterility occurred in animals following oral administration of epichlorohydrin, it is probable that similar effects would be produced by inhalation, since severe systemic effects have been observed after both dermal and inhalation exposures. [25,27] Epstein et al [61] did not observe any increase in the frequency of dead implantations in the uteri of mice following ip injections of 150 mg/kg of epichlorohydrin into the male rats mated to the females, nor did they provide any evidence of reduced fertility at this dosage.

Mutagenic effects of epichlorohydrin have been observed in microbial organisms and in the eukaryotic fruit fly, Drosophila melanogaster, following exposure to epichlorohydrin. [70] The number of point mutations observed in several microbial species increased as a function of epichlorohydrin concentration and duration of exposure. At present, an experimental relationship between the frequency of dead implantations and that of point mutations has not been observed. The positive results from the point mutation test systems in lower organisms, such as bacteria, [73-76] fungi, [71] and Drosophila melanogaster, [70] indicate that an increased risk of occurrence of point mutations may exist in human

populations exposed to epichlorohydrin. The fact that preparations derived from the urine of workers exposed to 25 ppm of epichlorohydrin influenced the genetic mechanisms in Salmonella typhimurium (DJ Kilian, written communication, April 1976) is consistent with the existence of a genetic risk to human populations exposed to epichlorohydrin.

The total risk to the health of employees occupationally exposed to epichlorohydrin is the result of the independent risks due to carcinogenesis, mutagenesis, sterility, and damage to kidneys, liver, respiratory tract, and to the skin. At present, evidence for the existence of the risks, other than to skin depends primarily on data from experimental animal models. Concern for employee health requires that the probability of the occurrence of chronic effects be minimized. NIOSH recommends, therefore, that worker exposure to epichlorohydrin be limited to a concentration of 2 mg/cu m (0.5 ppm) as a TWA concentration. This value has been chosen on the basis of professional judgment, rather than on quantitative data which clearly distinguish no-effect concentrations from those at which adverse effects have been shown to occur in human populations. A TWA concentration of 2 mg/cu m of epichlorohydrin should protect the employee against injury to organs during the individual's working lifetime, according to existing information. However, additional research is needed to provide support for the recommended environmental limit or to indicate the need for a different limit. The environmental limit implicitly assumes that the absorbed epichlorohydrin molecules will be detoxified by biochemical mechanisms, thereby reducing the risk of induction of human disease resulting from the cumulative toxicity of epichlorohydrin.

It is recognized that many employees handle small amounts of epichlorohydrin or work in situations where, regardless of the amount used, there is only negligible contact with epichlorohydrin. Under these conditions, it should not be necessary to comply with all of the provisions of the recommended standard, which has been prepared primarily to protect employee health under all circumstances. For these reasons, "occupational exposure to epichlorohydrin" is defined as exposure above one-half the TWA environmental limit, thereby delineating those work situations which do not require the expenditure of resources for environmental monitoring and associated recordkeeping. Because of nonrespiratory hazards such as the production of burns on the skin in the use of epichlorohydrin, NIOSH recommends that appropriate work practices and protective measures to limit such contact be required regardless of the concentration of airborne epichlorohydrin. Further, the observation of changes in the concentration of biochemical constituents [48] following human and animal exposure to epichlorohydrin suggest that the health of the exposed workers be monitored frequently. Thus, it is recommended that comprehensive medical examinations be offered to all employees subject to occupational exposure to epichlorohydrin and that the responsible physician consider the advisability of also administering any liver and kidney function tests.

VI. WORK PRACTICES

Work practices must be designed to minimize or to prevent inhalation of epichlorohydrin and skin and eyes from coming into contact with epichlorohydrin. Good work practices are a primary means of controlling certain exposures and will often supplement other control measures.

Enclosure of materials, processes, and operations is completely effective as a control only when the integrity of the system is maintained. Such systems should be inspected frequently for leaks and any leaks found should be promptly repaired. Special attention should be given to the condition of seals and joints, access ports, and other such places. [101] Similarly, points of wear should be inspected regularly for damage.

Ventilation systems require regular inspection and maintenance to ensure their effective operation. The effects of any changes or additions to the ventilating system or to the operations being ventilated should be assessed promptly, including measurements of airflow and of environmental levels of epichlorohydrin under the new conditions. Work practices should not introduce obstructions or interferences which would reduce the effectiveness of the ventilating system.

A major hazard of handling epichlorohydrin that can be minimized by good work practice is that from skin contact. Observation of animals indicates that severe systemic poisoning and death may result from skin contact with epichlorohydrin. [25,27] Ippen and Mathies [35] reported several cases of severe chemical burns caused by dermal contact with epichlorohydrin. Brief skin contact causes chemical burns, while extended skin contact may cause extensive skin burns and severe systemic effects.

The authors [35] also reported the occurrence of severe burns in an individual who spilled epichlorohydrin on his shoes which were not immediately removed. The severe effects are intensified by the penetration of epichlorohydrin into the clothing and shoes which act as reservoirs and continue the contact. For this reason, clothing contaminated with epichlorohydrin must be removed immediately and thoroughly laundered before reuse. Shoes on which epichlorohydrin is spilled are to be rendered unusable and discarded. The protective clothing must be made of material not permeable to epichlorohydrin. Penetration through three types of rubber has been measured [3] and found to be 9-11 minutes for nitrile rubber, 20-22 minutes for neoprene rubber, and 38-43 minutes for natural rubber. Since the penetration time is dependent on both the type of the rubber and the thickness, it is noteworthy that in this test [3] the thickness for each type of rubber was: 0.015 inches for nitrile rubber, 0.02 inches for neoprene rubber, and 0.030 inches for natural rubber. Since uniform thickness was not used, the data provide only a rough estimate of relative rate of epichlorohydrin penetration through different types of rubber. Nevertheless, it is evident that epichlorohydrin does penetrate rubber. When it is necessary to work with liquid epichlorohydrin, special handling techniques should be employed routinely. All body surfaces should be protected against contact with the liquid by the use of gloves, aprons, face shields, goggles, and other protective equipment or clothing. Ippen and Mathies [35] have pointed out that enclosed processes minimize any exposures; therefore, engineering controls are the most suitable control measures. Closed systems operating under negative pressure are particularly effective.

The flash point of epichlorohydrin is 93 F (70 C). [2] It is classified, therefore, as a flammable liquid of Class IC in 29 CFR 1910.106(a)(19)(iii). The lower and upper explosive limits in air at 20 C are 3.8 and 21.0%, respectively. [2] Hence, fire is a potential hazard because of the presence of epichlorohydrin. Recommended work practices should ensure that no flames or other sources of ignition, such as smoking, be permitted in the area where epichlorohydrin is stored or handled.

Safety showers, eyewash fountains, and fire extinguishers shall be located in or near areas where epichlorohydrin splashes are likely to occur and shall be properly maintained. Handwashing facilities, soap, and water must be available to the employees. As good hygiene practices, eating in epichlorohydrin work areas shall be prohibited and handwashing before eating recommended.

In summary, precautions must be exercised against overexposure to epichlorohydrin. It is important that employees be informed before job placement of hazards associated with the use of epichlorohydrin and when any process changes are made that may alter their epichlorohydrin exposure. Appropriate emergency procedures should be stressed. Recommended labels and posters must be displayed. The US Department of Labor "Material Safety Data Sheet," or a similar OSHA-approved form, must be filled out. In addition, all employees in the epichlorohydrin area should know where the safety sheet is posted. If all these work practices are observed and good engineering controls are installed, employees working with epichlorohydrin should be adequately protected from hazards associated with epichlorohydrin.

VII. RESEARCH NEEDS

Epidemiologic Study

One epidemiologic study involving workers exposed to epichlorohydrin has been found (DJ Kilian, written communication, April 1976). However, deficiencies such as the lack of a control group, the absence of measurements of exposure concentrations, and failure to indicate people lost to observation have limited the usefulness of the study. A retrospective controlled cohort study of a working population exposed chiefly to epichlorohydrin for a longer duration should provide valuable information.

Mutagenic Effect

This effect must be systematically investigated in greater depth with respect to dose, time, and route in both lower organisms and mammals. Animal tests using various doses, schedules, and routes of administration should be performed to see whether epichlorohydrin is a mutagen in mammals. Specific locus tests or heritable translocations should be considered. Animals should also be tested to see whether epichlorohydrin has any cytogenic effects.

Kidney Function in Workers Exposed to Epichlorohydrin

The impairment of kidney function as a result of epichlorohydrin exposure has been found in animals. As yet, there is no evidence that such injury also occurs in workers exposed to epichlorohydrin. Since a segment

of a working population which is exposed primarily to epichlorohydrin can be identified, kidney function tests should be given periodically to determine whether any changes in kidney function are occurring as a result of occupational exposure to epichlorohydrin.

Skin Sensitization

Although epichlorohydrin is commonly stated to be a sensitizer of the skin, the data that have been found in this regard are far from complete or persuasive. [11,36] Additional information on the degree and character of sensitization of the skin of humans is highly desirable. Some measure of variability in the skin response would be most useful.

Electroencephalographic (EEG) Studies

The index of effect by epichlorohydrin on humans that seems to be the most sensitive on the basis of the available information is a change in the voltage of the alpha rhythm of the EEG. [28] More information on the dose-response relationship for this effect and on its correlation with more usual alterations of function would be of great value.

Chronic Animal Exposure Studies

Inhalation exposure of various species of animals at several concentrations of epichlorohydrin up to the maximum tolerated concentration, 8 hours/day, 5 days/week, for at least 2 years, is recommended. These experiments should include measurement of food intake, monitoring of several biochemical parameters, gross and histopathologic

examinations of important organs and tissues including at least the liver, kidneys, respiratory tract, and CNS.

Metabolism and Distribution

The pathways of distribution and of elimination of epichlorohydrin as a function of dose route and dose rate in mammals have not been investigated. It is critical to determine which fraction of the dose reacts with the functionally essential biomolecules and which fraction is inactivated by detoxifying reactions. Both in vivo and in vitro studies should be conducted to determine the pathways. It is critical to determine the concentration at which reaction with functional biomolecules is a linear function of dose in intact animals.

Chemical Reactivity Toward all Classes of Biologic Nucleophiles

To acquire a better understanding of the reaction of epichlorohydrin with cells and organelles, experiments to determine its reaction with various classes of nucleophiles found in biologic systems should be carried out.

Hypertension

Kidney damage is often accompanied by hypertension. Since epichlorohydrin causes kidney damage in animals, studies should be conducted to see whether hypertension is also induced by epichlorohydrin exposure.

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IX. APPENDIX I

METHOD FOR SAMPLING EPICHLOROHYDRIN IN AIR

The following sampling method is adapted from those described by White et al [89] and in Method No. S118 of the Physical and Chemical Analysis Branch of NIOSH. [90]

Atmospheric Sampling

Collect breathing zone or personal samples representative of the individual employee's exposure. At the time of sample collection, record a description of sampling location and conditions, equipment used, time and rate of sampling, and any other pertinent information. Collect enough samples to permit calculation of a TWA exposure for every operation or location in which there is exposure to epichlorohydrin.

(a) Equipment

The sampling train consists of a charcoal tube and a vacuum pump.

(1) Charcoal tubes: Glass tubes, with both ends flame-sealed, 7-cm long with a 6-mm OD and a 4-mm ID, containing two sections of 20/40 mesh activated charcoal separated by a 2-mm portion of polyurethane foam. The primary section contains 100 mg of charcoal, the backup section, 50 mg. A 3-mm portion of polyurethane foam is placed between the outlet end of the tube and the backup section. A plug of glass wool is placed in front of the primary section. Tubes with the above specifications are commercially available.

(2) Pump: A battery-operated pump, complete with clip for

attachment to the employee's belt, capable of operating at 200 ml/minute or less.

(b) Calibration

The accurate calibration of a sampling pump is essential to the correct interpretation of the volume sampled. The frequency of calibration is dependent on the use, care, and handling to which the pump is subjected. Pumps should also be recalibrated if they have been misused or if they have just been repaired or received from a manufacturer. If the pump receives hard usage, more frequent calibration may be necessary. Maintenance and calibration should be performed on a regular schedule and records of these should be kept.

Ordinarily, pumps should be calibrated in the laboratory both before they are used in the field and after they have been used to collect a large number of field samples. The accuracy of calibration is dependent on the type of instrument used as a reference. The choice of calibration instrument will depend largely upon where the calibration is to be performed. For laboratory testing, a soapbubble meter is recommended, although other standard calibrating instruments can be used. The actual setups will be similar for all instruments.

Instructions for calibration with the soapbubble meter follow. If another calibration device is selected, equivalent procedures should be used. The calibration setup for personal sampling pumps with a charcoal tube is shown in Figure XIII-2. Since the flowrate given by a pump is dependent on the pressure drop across the sampling device, in this case a charcoal tube, the pump must be calibrated while operating with a representative charcoal tube in line.

(1) Check the voltage of the pump battery with a voltmeter to assure adequate voltage for calibration. Charge the battery if necessary.

(2) Break the tips of a charcoal tube to produce openings of at least 2 mm in diameter.

(3) Assemble the sampling train as shown in Figure XIII-2.

(4) Turn on the pump and moisten the inside of the soapbubble meter by immersing the buret in the soap solution. Draw bubbles up the inside until they are able to travel the entire buret length without bursting.

(5) Adjust the pump flowmeter to provide the desired flowrate.

(6) Check the water manometer to ensure that the pressure drop across the sampling train does not exceed 2.5 inches of water at 200 ml/minute.

(7) Start a soapbubble up the buret and measure with a stopwatch the time it takes the bubble to move from one calibration mark to another.

(8) Repeat the procedure in (7) above at least three times, average the results and calculate the flowrate by dividing the volume between the preselected marks by the time required for the soapbubble to traverse the distance. If, for the pump being calibrated, the volume of air sampled is calculated as the product of the number of strokes times a stroke factor (given in units of volume/stroke), the stroke factor is the quotient of the volume between the two preselected marks divided by the number of strokes.

(9) Data for the calibration include the volume measured, elapsed time or number of strokes of the pump, pressure drop, air temperature, atmospheric pressure, serial number of the pump, date, and name of the person performing the calibration.

(c) Sampling Procedure

(1) Break both ends of the charcoal tube to provide openings of at least 2 mm, which is half the ID of the tube. A smaller opening causes a limiting orifice effect which reduces the flow through the tube. The smaller section of charcoal in the tube is used as a backup section and therefore is placed nearest the sampling pump. Use tubing to connect the back of the tube to the pump, but tubing must never be put in front of the charcoal tube. The tube is supported in a vertical position in the employee's breathing zone.

(2) Sample a maximum of 20 liters of air at a flowrate of 200 ml/minute. For the determination of ceiling concentrations the sampling time is 15 minutes.

(3) Measure and record the temperature and pressure of the atmosphere being sampled.

(4) Treat at least one charcoal tube in the same manner as the sample tubes (break, seal, and ship), except draw no air through it. This tube serves as a blank.

(5) Immediately after samples are collected, cap the charcoal tubes with plastic caps. Do not use rubber caps. To minimize breakage during transport, pack capped tubes tightly in a shipping container.

X. APPENDIX II

ANALYTICAL METHOD FOR EPICHLOROHYDRIN

The following analytical method is adapted from those described by White et al, [89] by R Hill (written communication, June 1976), and in Method No. S118 of the Physical and Chemical Analysis Branch of NIOSH. [90]

Principle of the Method

Epichlorohydrin vapor trapped on charcoal from a known volume of air is desorbed with carbon disulfide. An aliquot of the desorbed sample is injected into a gas chromatograph. The area of the resulting peak is determined and compared with those obtained from injection of standards.

Range and Sensitivity

This method was developed to analyze epichlorohydrin over the range of 11.7-43.1 mg/cu m at an atmospheric temperature and pressure of 23 C and 765 mmHg. [90] For a 20-liter sample, the useful range of this method was 2-60 mg/cu m at a detector sensitivity that gives nearly full deflection on the strip chart recorder for a 1-mg sample. The method is capable of measuring smaller amounts down to 50 ppb, as demonstrated by Hill (written communication, June 1976). Desorption efficiency must be determined over the range used.

The upper limit of the range of the method is dependent on the absorptive capacity of the charcoal tube. This capacity varies with the

concentrations of epichlorohydrin and other substances in the air. The first section of the charcoal tube held at least 2 mg of epichlorohydrin when a test atmosphere containing 43.1 mg/cu m of epichlorohydrin in air was sampled at 0.185 liter/minute for 240 minutes; at that time, the concentration of epichlorohydrin in the effluent was less than 5% of that in the influent.

Interferences

Any compound which has about the same retention time as epichlorohydrin under the gas-chromatographic conditions described in this method will interfere with the analysis. This type of interference can be overcome by changing the operating conditions of the instrument, usually the column, the column temperature, or both. Epichlorohydrin appears to be stable under 80% humidity conditions.

Precision and Accuracy

In a collaborative test, the total relative error at 5 ppm epichlorohydrin (18.9 mg/cu m) was 0.7%. However, definition of total relative error was not given. Hill (written communication, June 1974) has determined that it is possible to analyze down to 0.25 μg/liter. Samples were collected from an 80% relative humidity atmosphere containing epichlorohydrin. Following a storage period of 14 days, the charcoal tubes were analyzed. The results of the analyses of two sets were 8.07 ± 0.25 and 11.64 ± 0.32 μg/tube. Hill found that the percent relative standard deviation of each set, which reflects the precision of the total sampling

and analytical procedure, was 7.21 and 5.33%, respectively. Under these conditions, the desorption efficiency was estimated to be 82.7%.

Apparatus

(a) Gas chromatograph equipped with a flame ionization detector.

(b) Stainless steel column (12 feet x 1/8 inch) with 10% carbowax 20 M stationary phase on 80/100 mesh acid-washed DMCS Chromosorb W solid support. Another column that can be used is stainless steel (6 feet x 2-mm ID) with 80/100 mesh Chromosorb 101. Other columns which achieve the desired separation may be used.

(c) A mechanical or electronic integrator or a recorder for determining peak area.

(d) Small glass-stoppered test tubes or equivalent.

(e) A 10-μl syringe and other conveniently sized syringes for preparation of the standards.

(f) Delivery pipets, 1.0-ml pipets.

Reagents

(a) Carbon disulfide, chromatographic quality.

(b) Epichlorohydrin, reagent grade.

(c) Helium, Bureau of Mines Grade.

(d) Hydrogen, purified.

(e) Compressed air, filtered.

Analysis of Samples

All glassware used for the laboratory analysis should be washed in detergent and rinsed with tap and distilled water.

(a) Preparation: Score each charcoal tube, including the blank from field samples, with a file and break open in front of the first section of charcoal. Remove and discard the glass wool. Transfer the charcoal in the first (larger) section to a small stoppered test tube. Remove and discard the foam separating sections and transfer the second section of charcoal to another test tube. Analyze the two charcoal sections separately.

(b) Desorption: Prior to analysis, pipet 1.0 ml of carbon disulfide into each test tube to desorb the epichlorohydrin from the charcoal. Desorption is complete in 30 minutes if the sample is stirred occasionally.

EXTREME CAUTION MUST BE EXERCISED AT ALL TIMES WHEN USING CARBON DISULFIDE BECAUSE OF ITS HIGH TOXICITY AND FIRE AND EXPLOSION HAZARDS. IT CAN BE IGNITED BY HOT STEAM PIPES. ALL WORK WITH CARBON DISULFIDE MUST BE PERFORMED UNDER AN EXHAUST HOOD.

(c) Typical gas chromatographic operating conditions for Chromosorb 101 column:

(1) 20 ml/minute helium flowrate.

(3) 200 C injector temperature.

(3) 230 C manifold temperature (detector).

(4) 135 C isothermal oven or column temperature.

(d) Injection: The first step in the analysis is the injection of the sample into the gas chromatograph. Employ the solvent flush injection technique. This eliminates difficulties arising from blowback or distillation within the syringe needle, thus increasing the accuracy and reproducibility of the injected sample volume. First, flush the 10.0-μl syringe with solvent several times to wet the barrel and plunger, then draw 3.0 μl of solvent into the syringe. Next, remove the needle from the carbon disulfide and pull the plunger back about 0.2 μl to separate the solvent flush from the sample with an air pocket to be used as a marker. Immerse the needle in the sample and withdraw a 5.0-μl portion, taking into consideration the volume of the needle since the sample in the needle will be completely injected. After the needle is removed from the sample and prior to injection in the gas chromatograph, pull the plunger back a short distance to minimize sample evaporation from the tip. Make duplicate injections of each sample and of the standard. No more than a 3% difference between the peak areas of the similar samples should be accepted as a valid result.

(e) Measurement of area: The areas of the sample peaks are measured by electronic integration or some other suitable method of area measurement. Preliminary sample results are read from a standard curve prepared as outlined below.

Determination of Desorption Efficiency

The desorption efficiency of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus, it is necessary to determine at least once the percentage of

epichlorohydrin that is removed in the desorption process. Repeat this procedure for each new batch of charcoal used.

Place the same amount of activated charcoal as in the first section of the sampling tube (100 mg) into a 5-cm, 4-mm ID glass tube; flame seal at one end. This charcoal must be from the same batch as that used in sampling and can be obtained from unused charcoal tubes. Cap the open end with Parafilm or equivalent. Inject a known amount of hexane solution containing 94.5 mg/ml of epichlorohydrin directly into the activated charcoal with a microliter syringe and cap the tube with more Parafilm or equivalent.

Prepare at least five tubes in this manner and allow to stand overnight or longer to ensure complete adsorption of the epichlorohydrin on the charcoal. These five tubes are referred to as the samples. Treat a parallel blank tube in the same manner, except add no epichlorohydrin to it. Desorb and analyze the sample and blank tubes in exactly the same manner as the sampling tube described for unknown air samples.

Prepare two or three standards by injecting the same volume of epichlorohydrin into 1.0 ml of carbon disulfide with the same syringe used in the preparation of the sample. These are analyzed with the samples.

The desorption efficiency equals the difference between the average peak area of the samples and that of the blank divided by the average peak area of the standards, or:

$$\text{desorption efficiency} = \frac{\text{average weight recovered (mg)}}{\text{weight added (mg)}}$$

Calibration and Standards

It is convenient to express the concentration of standards in terms of mg/ml of carbon disulfide because samples are desorbed in 1 ml of carbon disulfide. Use the density of epichlorohydrin to convert milligrams into microliters for easy measurement with a microliter syringe. Prepare a series of standards varying in concentration over the range of interest and then analyze under the same gas-liquid chromatographic conditions and during the same time period as the unknown samples. Prepare standard curves by plotting concentration in mg/ml versus peak area.

Calculations

Read the weight in milligrams corresponding to the total peak area from the standard curve. No volume corrections are needed because the standard curve is based on mg/ml carbon disulfide and the volume of sample injected is identical to the volume of the standards injected.

Make corrections for the blank from the field sampling for each sample by subtracting the amounts of epichlorohydrin found on the front and back sections of the blank from the amounts found in the respective sections of the sample:

corrected amount = amount on sample - amount on blank

Add the corrected amounts present in the front and in the backup sections of the same sample tube to determine the total amount of epichlorohydrin in the sample. Divide this total amount by the desorption

efficiency to obtain the adjusted total amount of epichlorohydrin in the sample:

$$\text{adjusted total amount} = \frac{\text{total amount}}{\text{desorption efficiency}}$$

The concentration of epichlorohydrin in the air sampled, expressed in mg/cu m, is given by the quotient of the adjusted amount in mg divided by the volume of air sampled in cu m:

$$\text{concentration (mg/cu m)} = \frac{\text{adjusted amount (mg)}}{\text{volume (cu m)}}$$

Another method of expressing concentration is ppm:

$$\text{concentration (ppm)} = \text{concentration (mg/cu m)} \times \frac{24.45}{MW} \times \frac{760}{P} \times \frac{(T + 273)}{298}$$

where:

24.45 = molar volume (liter/mole) at 25 C and 760 mmHg

760 = standard pressure

P = pressure (mmHg) of air sampled

T = temperature (degrees C) of air sampled

MW = molecular weight of epichlorohydrin (g/mole)

298 = standard temperature (degrees K)

XI. APPENDIX III

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or

competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that an MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flashpoint, shock sensitivity,

or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 degrees Fahrenheit (21.1 degrees Celsius); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50, if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement, if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

Skin Contact--causes delayed burns.

Eye Contact--some pain and transient irritation.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill" or "incineration." Warnings such as "comply with local, state, and federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or US Bureau of Mines approval class, ie, "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

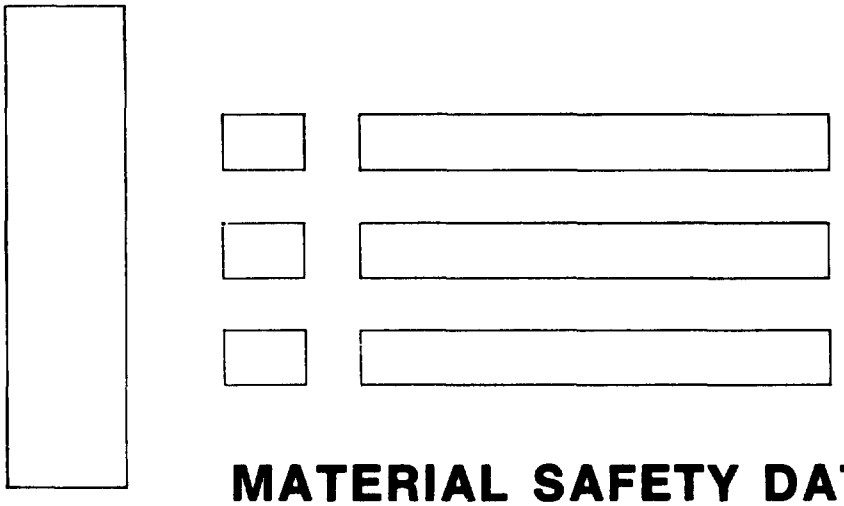
(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees potentially exposed to the hazardous material. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.



MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO. EMERGENCY TELEPHONE NO.
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA			
BOILING POINT 760 MM HG		MELTING POINT	
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE	
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT	
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE=1)	
APPEARANCE AND ODOR			

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN:

INHALATION:

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY _____

ADDRESS: _____

DATE _____

XII. APPENDIX IV

GLOSSARY*

ALKYLATING AGENTS - Agents capable of introducing an alkyl radical into an organic or inorganic molecule by forming a stable carbon covalent bond.

BASE-PAIRING RULES - The requirement that adenine must always form a base pair with thymine (or uracil) and guanine with cytosine, in a nucleic acid double helix.

BASE-PAIR SUBSTITUTION MUTATION - A change of one base pair for another base pair, eg, A--T to G--C.

DELETIONS - Loss of a section of the genetic material from a chromosome. The size of the deleted material can vary from a single nucleotide to sections containing a number of genes.

DNA (Deoxyribonucleic Acid) - A polymer of deoxyribonucleotides. The genetic material of all cells.

FRAMESHIFT MUTATIONS - Either deletions or additions of one or more but not three or a multiple of three base pairs. In the case of deletion, reading of the codon is shifted forward one base and in the case of addition, the reading is shifted back one base.

MUTAGENS - Physical or chemical agents, such as radiation, heat, and alkylating or deaminating agents, which may increase the frequency of mutation above the observed spontaneous frequency.

MUTATION - An inheritable change in a nucleic acid.

NUCLEOPHILE - An atom or a molecule which can share a pair of electrons with an electropositive center in order to form a covalent bond.

POINT MUTATION - Alteration in DNA affecting one or a very small number of nucleotides. These alterations can be divided into two main subgroups: frameshift mutations and base-pair substitution mutations.

REVERSE (BACK) MUTATION - An inheritable change in a mutant gene that restores the original biologic function and, in some cases, the original nucleotide sequence.

SPONTANEOUS MUTATIONS - Mutations for which there is no "observable" cause.

SUPPRESSOR MUTATION - A mutation that totally or partially restores a function lost by a primary mutation and is located at a genetic site different from the primary mutation.

TRANSLOCATION - The transfer of a section of one chromosome to a nonhomologous chromosome.

TRANSDUCTION - Transfer of a portion of one gene to another gene by movement of DNA.

TRANSITION MUTATION - The replacement of a purine by a different purine or a pyrimidine by a different pyrimidine in a nucleic acid sequence.

TRANSVERSION MUTATION - The replacement of a purine by a pyrimidine or of a pyrimidine by a purine.

WILD-TYPE GENE - The form of gene (allele) commonly found in nature.

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*Adapted from references 68 and 69

XIII. TABLES AND FIGURES

TABLE XIII-1

PHYSICAL PROPERTIES OF EPICHLOROHYDRIN

Molecular formula	C_3H_5OCl
Formula weight	92.5
Boiling point	116.4 C
Melting point (freezing point)	-58.1 C
Vapor pressure	5 mmHg at 5.6 C 20 mmHg at 29 C 400 mmHg at 97.4 C
Specific gravity (20/4 C)	1.1839
Solubility	6.48% in water; soluble in acetone, benzene, ether, heptane, and methanol
Flashpoint (open cup)	93 F
Saturation concentration (in air at 25 C)	22,390 ppm
Lower explosive limit	3.8%
Upper explosive limit	21.0%
Autoignition temperature	416 C
Conversion factors (760 mmHg and 25 C)	1 ppm = 3.78 mg/cu m 1 mg/cu m = 0.26 ppm

Derived from references 2,4, and 5

TABLE XIII-2

INDICES OF INTOXICATION IN RATS SUBJECTED TO ONE 4-HOUR INHALATION EXPOSURE TO EPICHLOROHYDRIN AT VARIOUS CONCENTRATIONS

Dose (mg/l)	Day*	Body Temp (C)	02 Consumption (ml/hr)	Liver Weight Coefficient	BSP Test	Urine Volume (ml)	Specific Gravity of Urine	Chloride Content in Urine (mg/day)
0.35	0	33.4±0.34	235±23.3	4.26±0.18	8.6±0.30	-	-	-
	1	36.8±0.13	244±20.3	-	0.1	4.4±0.56	1.023±0.006	8.3±1.91
0.02	0	35.5±0.36	275±11.7	4.00±0.18	2.5±1.30	-	-	-
	1	36.7±0.20	281±16.7	-	3.8±0.20	4.0±0.54	1.016±0.002	5.5±0.54
0.007	0	36.2±0.15	331±19.4	4.11±0.26	1.4±0.40	-	-	-
	1	37.1±0.10	318± 4.8	-	2.8±0.20	4.9±0.65	1.009±0.002	7.1±1.15
Control	0	36.6±0.11	426±14.6	3.31±0.17	0.1	-	-	-
	1	36.9±0.09	410±15.4	-	0.1	2.6±0.72	1.030±0.007	3.6±0.90

*Observation made immediately after exposure (Day 0) or after 1 day (Day 1)

Adapted from reference 32

TABLE XIII-3

EVALUATION OF URINE
OF EPICHLOROHYDRIN-EXPOSED PERSONNEL FOR MUTAGENIC ACTIVITY

Subject	8-hr TWA Exposure (ppm)	Revertants (Treated)/Revertants (Control)				
		S typhimurium Strain				
		1535	1537	1538	100	98
PW1	0.8	1.11	0.88	1.69	1.91	1.78
CBS	1.2	0.96	1.11	0.69	1.21	1.73
TWW	1.2 (A)	1.27	0.93	1.72	0.87	0.83
	1.2 (B)	1.20	0.87	1.56	1.00	0.58
JJM	1.5	0.93	1.00	1.25	1.54	1.23
CBS	1.7 (A)	1.00	0.95	0.57	0.93	1.62
	2.6 (B)	0.80	0.84	0.66	0.93	1.31
PW1	3.2 (A)	1.16	0.67	1.22	2.00	1.62
	3.2 (B)	1.30	0.58	1.69	1.79	1.46
H	3.5	0.87	1.00	1.13	0.87	1.00
DDL	3.6	0.62	0.63	0.60	0.91	1.00
PW1	4.0	1.03	0.67	1.41	1.61	1.38
SJ*	exceeds 25**	2.48	0.24	1.12	0.99	-
GV*	exceeds 25**	2.64	0.53	1.12	1.13	-
	Average	1.24	0.78	1.17	1.26	1.21
	SD	±0.59	±0.24	±0.42	±0.42	±0.49

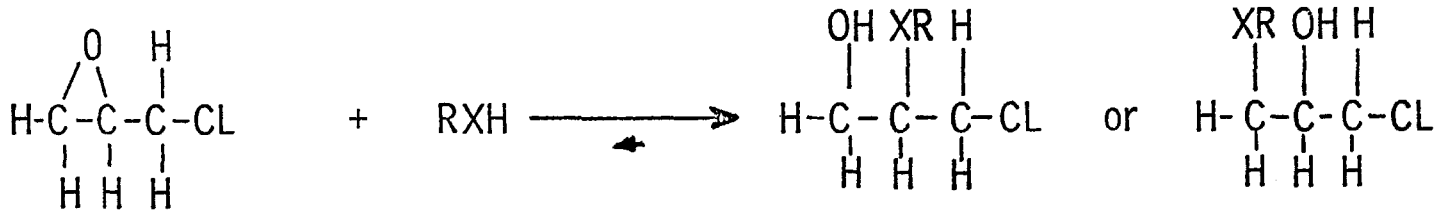
TABLE XIII-3 (CONTINUED)

EVALUATION OF URINE OF
EPICHLOROHYDRIN EXPOSED PERSONNEL FOR MUTAGENIC ACTIVITY

Subject	8-hr TWA Exposure (ppm)	Revertants (Treated)/Revertants (Control)				
		S typhimurium Strain				
		1535	1537	1538	100	98
WR	Control	1.24	0.54	0.88	1.00	1.08
RWV	"	0.86	1.04	1.19	1.58	1.00
SRR	"	0.89	0.13	0.94	1.70	0.76
LAS	"	1.08	0.42	1.22	2.21	1.03
L	"	0.78	0.63	0.98	0.57	0.89
	Average	0.97	0.55	1.04	1.41	0.95
	SD	±0.19	±0.33	±0.15	±0.64	±0.13

*Acute exposure
**Average area monitoring results during 105 min

From DJ Kilian (written communication, April 1976)



where X = an electronegative element such as oxygen nitrogen, or sulfur

where R = an alkyl or aryl or other organic group.

By the law of mass action, the rate of reaction of epichlorohydrin with a nucleophile is given by: .

$$\frac{d\,[CH_2OCHCH_2CL]}{dt} = k\,[CH_2OCHCH_2CL]\,[RXH]$$

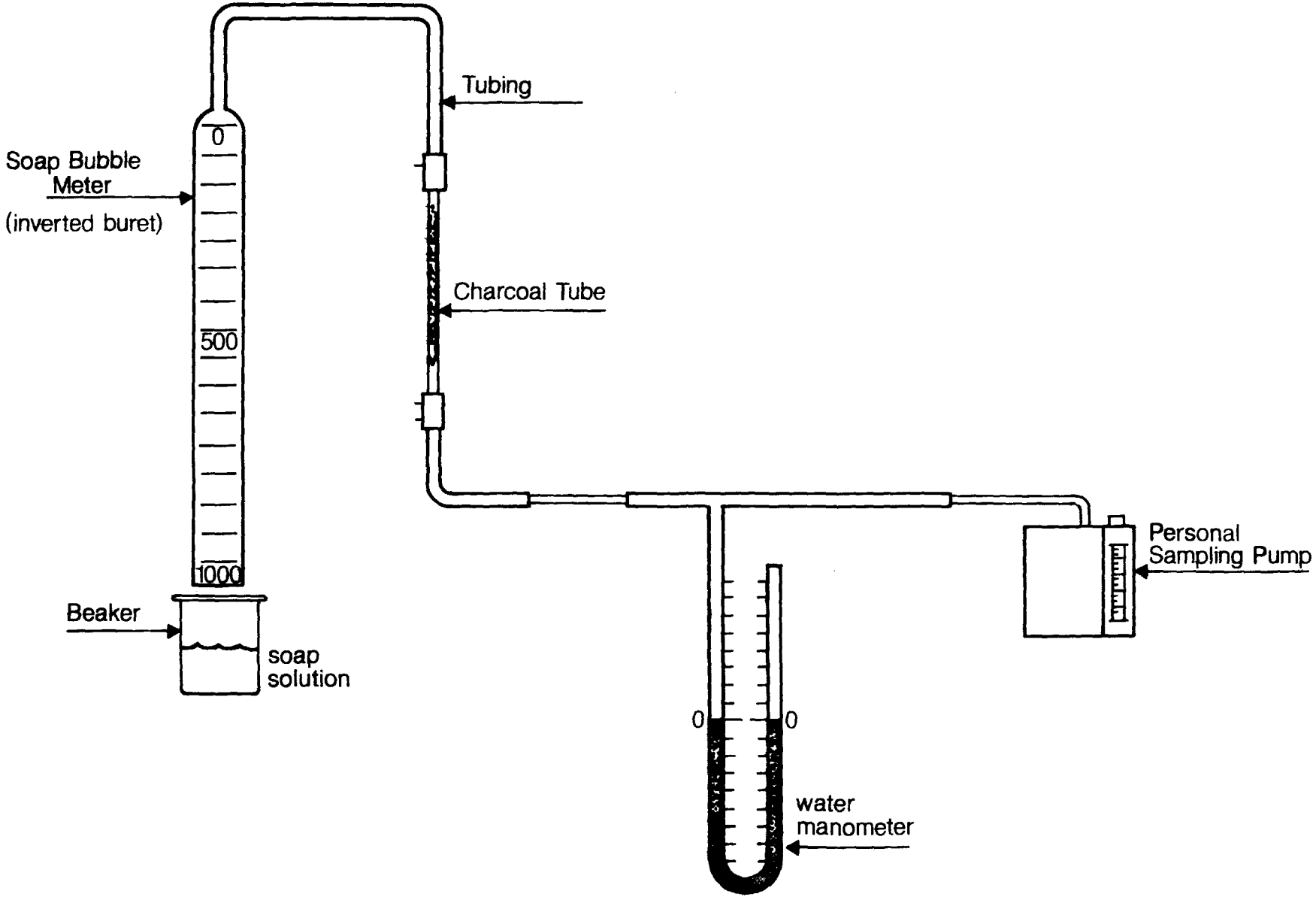
where k = a rate constant

Figure XIII-1

REACTION OF EPICHLOROHYDRIN

FIGURE XIII-2

CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP WITH CHARCOAL TUBE



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HEW Publication No. (NIOSH) 76-206